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18. June 2003

John Nielsen



AMINO-FUNCTIONAL CHALCONES

17 MAJ 2002

Modtaget

FIELD OF THE INVENTION

The present invention relates to a novel class of chalcone derivatives and analogues and to their use as pharmaceutically active agents, in particular against bacterial and parasitic
5 infections

Furthermore, the invention relates to a method of predicting whether a chemical compound has a potential inhibitory effect against an organism selected from *Helicobacter pylori* and *Plasmodium falciparum*. The prediction is based on the ability of the chemical
10 compound to act as an inhibitor of the enzyme dihydroorotate dehydrogenase which is involved in the synthesis of pyrimidine in prokaryotic as well as eukaryotic cells such as bacteria, parasites, fungi, helminths and any type of mammalian cells such as human cells

BACKGROUND OF THE INVENTION

Chalcones, e.g., for use against parasitic infections are known from earlier patent
15 applications assigned to the applicant, e.g. WO 93/17671 and WO 99/00114

The bioavailability for several of the known chalcones is low due to the low solubility of the compounds. The compounds do not typically dissolve in the intestine and are therefore not
20 available for absorption

The spread of antimicrobial resistance determinants particular among nosocomial bacterial pathogens is an increasing problem. Such resistant pathogens include *Staphylococcus aureus* resistant to methicillin and thus to all β -lactam-antibiotics and Enterococci resistant to vancomycin (VRE). Such resistant bacteria pose a significant therapeutic challenge and
25 bacterial strains resistant to all currently available antimicrobials are emerging. Furthermore, bacterial species intrinsically resistant to commonly employed antimicrobials are being recognized as important opportunistic pathogens in the setting of long-term immunocompromized patients. An example of this is *Stenotrophomonas maltophilia* which possesses a β -lactamase rendering the bacteria intrinsically resistant to carbapenems. As
30 cross-resistance within a given class of antibiotics often occurs the development of new classes of antibiotics is a necessity to counter the emerging threat of bacterial resistance

Thus, there is a need for improved chalcone derivatives for therapeutic or prophylactic use against parasites and bacteria

35 BRIEF DESCRIPTION OF THE FIGURES

Figure 1 illustrates the general synthetic scheme for the preparation of amino-functional chalcones where the aromatic rings are phenyl rings. R^1 , R^2 , and Z are as defined herein

Figure 2 illustrates the synthesis of amino-dihydrochalcones. R^1 , R^2 , and Z are as defined
40 herein

Figure 3 illustrates a time-kill curve of II-105 against *S aureus* ATCC29213. Bacterial growth is inhibited at concentrations at or above the MIC (MIC=18.8 μ M). As CFU counts per ml decreases at concentrations of compound above the MIC, the compound is bactericidal. The reduction in CFU/ml is faster as the concentration of test compound increases above the MIC. This indicates that the bactericidal action of the compound is primarily dependent on the concentration of the test compound.

Figure 4 illustrates a time-kill curve of II-056 against *S aureus* ATCC29213. Bacterial growth is inhibited at concentrations of test compound at or above the MIC (MIC=9.4 μ M). As CFU counts per ml decreases at concentrations of compound above the MIC, the compound is bactericidal. The rate of reduction of CFU/ml is not significantly affected by increasing concentrations of test compound. Thus, the bactericidal action of the compound is primarily dependent on incubation time.

Figure 5 illustrates a dose-response curve of LicA and one of the novel amino-chalcones (II-123) at *Plasmodium falciparum*. As shown in the figure, II-123 is 45 times more potent than LicA.

20 DESCRIPTION OF THE INVENTION

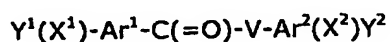
The present inventors have found that the amino-functional chalcone defined herein exhibit interesting biological properties combined with improved metabolic and physicochemical properties which make the compound useful as drug substances, in particular as antiparasitic agents, bacteriostatic agents, and bacteriocidal agents.

It is believed that the amino group or groups of the amino-functional chalcone will be charged according to pH of the medium and the pKa of the compound. The solubility of the charged compounds is many times higher than the solubility of the neutral compounds. As the amino-functional chalcones will be partially charged (i.e. soluble) at the pH in the intestine, they will dissolve in the gastric juices and be available for absorption. The bioavailability of the amino-functional chalcones will therefore be improved many times compared to the known neutral chalcones making the compounds generally useful as drug candidates. Also, the amino-functional chalcones have different pKa values which enable the selection of a chalcone derivative with optimal charged/non-charged ratio at a given pH value.

The usefulness of the known chalcones as drug candidates have been limited by the metabolism of the compounds resulting in short half-lives *in vivo*. The inventors have now found that introduction of an amino group in the chalcone derivative changes the metabolic properties and the compounds prepared show improved metabolic stability.

Futhermore, the inventors have found that the amino-functional chalcones defined herein exhibit excellent bacteriocidal and bacteriostatic properties, even against multi-resistant bacteria strains

- 5 Thus, the present invention provides chalcone derivatives and analogues as defined in claim 1, i e a compound of the general formula



- 10 wherein Ar^1 and Ar^2 independently are selected from aromatic rings (aryl) and heteroaromatic rings (heteroaryl),

V designates $-CH_2-CH_2-$, $-CH=CH-$ or $-C\equiv C-$, preferably $-CH=CH-$,

- 15 one or both of Y^1 and Y^2 independently represent at least one, such as 1-2, e g one, amino-functional substituent(s) of the formula



- 20 wherein Z is a biradical $-(C(R^H)_2)_n-$, wherein n is an integer in the range of 1-6, preferably 1-4, such as 1-3, and each R^H is independently selected from hydrogen and C_{1-6} -alkyl, or two R^H on the same carbon atom may designate =O,

- R^1 and R^2 independently are selected from hydrogen, optionally substituted C_{1-12} -alkyl, 25 optionally substituted C_{2-12} -alkenyl, optionally substituted C_{4-12} -alkadienyl, optionally substituted C_{6-12} -alkatrienyl, optionally substituted C_{2-12} -alkynyl, optionally substituted C_{1-12} -alkoxycarbonyl, optionally substituted C_{1-12} -alkylcarbonyl, optionally substituted aryl, optionally substituted aryloxycarbonyl, optionally substituted arylcarbonyl, optionally substituted heteroaryl, optionally substituted heteroaryloxycarbonyl, optionally substituted 30 heteroarylcarbonyl, aminocarbonyl, mono- and di(C_{1-6} -alkyl)aminocarbonyl, amino- C_{1-6} -alkyl-aminocarbonyl, mono- and di(C_{1-6} -alkyl)amino- C_{1-6} -alkyl-aminocarbonyl, or R^1 and R^2 together with the nitrogen atom to which they are attached ($-N(R^1)R^2$) form an optionally substituted nitrogen-containing heterocyclic ring,

- 35 X^1 and X^2 independently designates 0-5, preferably 0-4, such as 0-3, e g 0-2, substituents, where such optional substituents independently are selected from optionally substituted C_{1-12} -alkyl, optionally substituted C_{2-12} -alkenyl, optionally substituted C_{4-12} -alkadienyl, optionally substituted C_{6-12} -alkatrienyl, optionally substituted C_{2-12} -alkynyl, hydroxy, optionally substituted C_{1-12} -alkoxy, optionally substituted C_{2-12} -alkenyloxy, 40 carboxy, optionally substituted C_{1-12} -alkoxycarbonyl, optionally substituted C_{1-12} -alkylcarbonyl, formyl, C_{1-6} -alkylsulphonylamino, optionally substituted aryl, optionally substituted aryloxycarbonyl, optionally substituted aryloxy, optionally substituted arylcarbonyl, optionally substituted arylamino, arylsulphonylamino, optionally substituted heteroaryl, optionally substituted heteroaryloxycarbonyl, optionally substituted

- heteroaryloxy, optionally substituted heteroarylcarbonyl, optionally substituted heteroarylamino, heteroarylsulphonylamino, optionally substituted heterocyclyl, optionally substituted heterocyclyloxycarbonyl, optionally substituted heterocyclyloxy, optionally substituted heterocyclylcarbonyl, optionally substituted heterocyclylamino,
- 5 heterocyclisulphonylamino, amino, mono- and di(C₁₋₆-alkyl)amino, carbamoyl, mono- and di(C₁₋₆-alkyl)aminocarbonyl, amino-C₁₋₆-alkyl-aminocarbonyl, mono- and di(C₁₋₆-alkyl)amino-C₁₋₆-alkyl-aminocarbonyl, C₁₋₆-alkylcarbonylamino, amino-C₁₋₆-alkyl-carbonylamino, mono- and di(C₁₋₆-alkyl)amino-C₁₋₆-alkyl-carbonylamino, cyano, guanidino, carbamido, C₁₋₆-alkanoyloxy, C₁₋₆-alkylsulphonyl, C₁₋₆-alkylsulphinyl, C₁₋₆-alkylsulphonyl-
- 10 oxy, aminosulfonyl, mono- and di(C₁₋₆-alkyl)aminosulfonyl, nitro, optionally substituted C₁₋₆-alkylthio, and halogen, where any nitrogen-bound C₁₋₆-alkyl may be substituted with hydroxy, C₁₋₆-alkoxy, C₂₋₆-alkenyloxy, amino, mono- and di(C₁₋₆-alkyl)amino, carboxy, C₁₋₆-alkylcarbonylamino, halogen, C₁₋₆-alkylthio, C₁₋₆-alkyl-sulphonyl-amino, or guanidine,
- 15 and salts thereof

The substituents R¹ and R² carried by the nitrogen atom of the amino substituent are believed to slightly alter the pKa value of the chalcone derivative. Thus, the particular selection of the groups R¹ and R² can be used to "fine-tune" the pKa value in view of the

20 particular condition or disease and the intended route of administration

In one embodiment, R¹ and R² are independently selected from hydrogen, optionally substituted C₁₋₁₂-alkyl, optionally substituted C₂₋₁₂-alkenyl, optionally substituted C₂₋₁₂-alkynyl, optionally substituted C₁₋₁₂-alkylcarbonyl, arylcarbonyl, heteroarylcarbonyl, amino-

25 carbonyl, mono- and di(C₁₋₆-alkyl)aminocarbonyl, amino-C₁₋₆-alkyl-aminocarbonyl, and mono- and di(C₁₋₆-alkyl)amino-C₁₋₆-alkyl-aminocarbonyl. In particular R¹ and R² are independently selected from hydrogen, optionally substituted C₁₋₆-alkyl, optionally substituted C₁₋₆-alkylcarbonyl, heteroarylcarbonyl, aminocarbonyl, mono- and di(C₁₋₆-alkyl)aminocarbonyl, amino-C₁₋₆-alkyl-aminocarbonyl, mono- and di(C₁₋₆-alkyl)amino-C₁₋₆-alkyl-aminocarbonyl

30 alkyl-aminocarbonyl

In another embodiment, R¹ and R² together with the nitrogen atom to which they are attached (-N(R¹)R²) form an optionally substituted nitrogen-containing heterocyclic ring

35 The selection of the substituents X¹ and X² is not very critical. Thus, it is believed that these substituents can be chosen fairly freely

However, in still a further embodiment, X¹ and X² independently designates 0-4, such as 0-3, e.g. 0-2, substituents, where such optional substituents independently are selected from

40 optionally substituted C₁₋₁₂-alkyl, hydroxy, optionally substituted C₁₋₁₂-alkoxy, optionally substituted C₂₋₁₂-alkenyloxy, carboxy, optionally substituted C₁₋₁₂-alkylcarbonyl, formyl, C₁₋₆-alkylsulphonylamino, optionally substituted aryl, optionally substituted aryloxy-carbonyl, optionally substituted aryloxy, optionally substituted arylcarbonyl, optionally substituted arylamino, arylsulphonylamino, optionally substituted heteroaryl, optionally

substituted heteroaryl-amino, optionally substituted heteroaryl-carbonyl, optionally substituted heteroaryl-oxy, heteroarylsulphonyl-amino, optionally substituted heterocycl-yl, optionally substituted heterocycl-oxy, optionally substituted heterocycl-yl-amino, amino, mono- and di(C₁₋₆-alkyl)-amino, carbamoyl, mono- and di(C₁₋₆-alkyl)-aminocarbonyl, amino-
 5 C₁₋₆-alkyl-aminocarbonyl, mono- and di(C₁₋₆-alkyl)-amino-C₁₋₆-alkyl-aminocarbonyl, C₁₋₆-alkyl-carbonyl-amino, amino-C₁₋₆-alkyl-carbonyl-amino, mono- and di(C₁₋₆-alkyl)-amino-C₁₋₆-alkyl-carbonyl-amino, guanidino, carbamido, C₁₋₆-alkylsulphonyl, C₁₋₆-alkylsulphinyl, C₁₋₆-alkylsulphonyloxy, optionally substituted C₁₋₆-alkylthio, aminosulfonyl, mono- and di(C₁₋₆-alkyl)-aminosulfonyl, and halogen, where any nitrogen-bound C₁₋₆-alkyl may be substituted
 10 with hydroxy, C₁₋₆-alkoxy, and/or halogen, in particular X¹ and X² independently designates 0-3, e.g. 0-2, substituents, where such optional substituents independently are selected from optionally substituted C₁₋₆-alkyl, hydroxy, optionally substituted C₁₋₆-alkoxy, carboxy, optionally substituted C₁₋₆-alkyl-carbonyl, C₁₋₆-alkylsulphonyl-amino, optionally substituted aryl, optionally substituted aryloxy, optionally substituted aryl-amino, arylsulphonyl-amino,
 15 optionally substituted heteroaryl, optionally substituted heteroaryl-amino, heteroaryl-sulphonyl-amino, amino, mono- and di(C₁₋₆-alkyl)-amino, carbamoyl, C₁₋₆-alkyl-carbonyl-amino, guanidino, carbamido, optionally substituted C₁₋₆-alkylthio, optionally substituted heterocycl-yl, optionally substituted heterocycl-oxy, optionally substituted heterocycl-yl-amino and halogen, where any nitrogen-bound C₁₋₆-alkyl may be substituted with hydroxy,
 20 C₁₋₆-alkoxy, and/or halogen

The group V is relevant with respect to the spatial orientation of the rings Ar¹ and Ar². Thus, the group V may be -CH₂-CH₂-, -CH=CH- or -C≡C-. Preliminary results have shown that the embodiments wherein V designates -CH=CH- yields valuable chalcone derivatives
 25

The expression "chalcone derivative" has been assigned to the compounds of the above formula in that the overall structure namely Ar¹-C(=O)-C-C-Ar² resembles that of the chalcone structure. This being said, Ar¹ and Ar² are selected from aromatic rings and heteroaromatic rings. It is currently believed that particularly interesting compounds are
 30 those where at least one of Ar¹ and Ar², preferably both, are aromatic rings, in particular phenyl rings. This being said, the inventors envisage that the functionality of the compounds may be substantially preserved (or even improved) when one or both of Ar¹ and Ar² are heteroaromatic rings

35 In one embodiment, at least one of Ar¹ and Ar² is selected from thiazolyl, pyrrolyl, imidazolyl, pyrazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, thiophenyl, quinolyl, isoquinolyl, and indolyl

In another embodiment, both of Ar¹ and Ar² are phenyl rings and Y¹ represent at least one
 40 amino-functional substituent

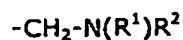
In a further embodiment, X² represents at least one substituent selected from C₁₋₆-alkyl, C₁₋₆-alkoxy, C₁₋₆-alkyl-carbonyl, optionally substituted aryl, optionally substituted aryloxy, optionally substituted aryl-amino, optionally substituted heteroaryl, optionally substituted

heteroaryl-amino, mono- and di(C₁₋₆-alkyl)-amino, C₁₋₆-alkyl-carbonyl-amino, optionally substituted C₁₋₆-alkyl-thio, optionally substituted heterocycl-yl, optionally substituted heterocycl-yloxy, optionally substituted heterocycl-yl-amino and halogen

- 5 The Z group represents the biradical between the ring and the amino functionality. This group Z is typically a biradical $-(C(R^H)_2)_n-$, wherein n is an integer in the range of 1-6, preferably 1-4, such as 1-3, where each R^H is independently selected from hydrogen and C₁₋₆-alkyl, or two R^H on the same carbon atom may designate =O. A particular example of Z is $-(CH_2)_n-$ wherein n is 1-4, such as 1-3.

10

Thus, in a particular embodiment, one of Y¹ and Y² represent a substituent of the formula



- 15 wherein R¹ and R² is selected from hydrogen and C₁₋₆-alkyl. Furthermore, V is preferably -CH=CH-, and Ar¹ and Ar² both are phenyl rings. In a particular embodiment, Y¹ represents the substituent to the formula $-CH_2-N(R^1)R^2$.

Definitions

20

In the present context, the term "bacterostatic" is intended to describe an antimicrobial activity of a test compound, characterized by an inhibition of bacterial growth in the absence of a reduction of viable bacteria (bacterial kill) during incubation with the test compound, as evidenced in the killing curve determination by a stationary number of

- 25 colony forming units (CFU) during incubation time.

In the present context, the term "bacteriocidal" is intended to describe an antimicrobial activity of a test compound, characterized by the reduction of viable bacteria (bacterial kill) during incubation with the test compound, as evidenced in the killing curve determination

- 30 by a reduction of colony forming units (CFU) during incubation time.

In the present context, the term "antiparasitic" is intended to describe the ability of a test compound to upon incubation in vitro with a culture of parasites, e.g. *Leishmania major* or *Plasmodium falciparum*, to inhibit metabolic labelling of the parasites by at least 50%

- 35 compared to mock treated control cultures.

- In the present context, the term "C₁₋₁₂-alkyl" is intended to mean a linear, cyclic or branched hydrocarbon group having 1 to 12 carbon atoms, such as methyl, ethyl, propyl, *iso*-propyl, cyclopropyl, butyl, *tert*-butyl, *iso*-butyl, cyclobutyl, pentyl, cyclopentyl, hexyl, cyclohexyl, etc. Analogously, the term "C₁₋₆-alkyl" is intended to mean a linear, cyclic or branched hydrocarbon group having 1 to 6 carbon atoms, such as methyl, ethyl, propyl, *iso*-propyl, pentyl, cyclopentyl, hexyl, cyclohexyl, and the term "C₁₋₄-alkyl" is intended to cover linear, cyclic or branched hydrocarbon groups having 1 to 4 carbon atoms, e.g. methyl, ethyl, propyl, *iso*-propyl, cyclopropyl, butyl, *iso*-butyl, *tert*-butyl, cyclobutyl.

heteroaryl-amino, heteroaryloxy, heteroarylcarbonyl, amino, mono- and di(C₁₋₆-alkyl)amino, carbamoyl, mono- and di(C₁₋₆-alkyl)aminocarbonyl, amino-C₁₋₆-alkyl-aminocarbonyl, mono- and di(C₁₋₆-alkyl)amino-C₁₋₆-alkyl-aminocarbonyl, C₁₋₆-alkylcarbonylamino, guanidino, carbamido, C₁₋₆-alkyl-sulphonyl-amino, C₁₋₆-alkyl-sulphonyl, C₁₋₆-alkyl-sulphinyl, C₁₋₆-alkylthio, halogen, where any aryl and heteroaryl may be substituted as specifically describe below for "optionally substituted aryl and heteroaryl"

Especially preferred examples are hydroxy, C₁₋₆-alkoxy, C₂₋₆-alkenyloxy, amino, mono- and di(C₁₋₆-alkyl)amino, carboxy, C₁₋₆-alkylcarbonylamino, halogen, C₁₋₆-alkylthio, C₁₋₆-alkylsulphonyl-amino, and guanidine

"Halogen" includes fluoro, chloro, bromo, and iodo

In the present context the term "aryl" is intended to mean a fully or partially aromatic carbocyclic ring or ring system, such as phenyl, naphthyl, 1,2,3,4-tetrahydronaphthyl, anthracyl, phenanthracyl, pyrenyl, benzopyrenyl, fluorenyl and xanthenyl, among which phenyl is a preferred example

The term "heteroaryl" is intended to mean a fully or partially aromatic carbocyclic ring or ring system where one or more of the carbon atoms have been replaced with heteroatoms, e.g. nitrogen (=N- or -NH-), sulphur, and/or oxygen atoms. Examples of such heteroaryl groups are oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyrrolyl, imidazolyl, pyrazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, triazinyl, coumaryl, furyl, thiophenyl, quinolyl, benzothiazolyl, benzotriazolyl, benzodiazolyl, benzooxazolyl, phthalazinyl, phthalanyl, triazolyl, tetrazolyl, isoquinolyl, acridinyl, carbazolyl, dibenzazepinyl, indolyl, benzopyrazolyl, phenoxazonyl. Particularly interesting heteroaryl groups are oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyrrolyl, imidazolyl, pyrazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, furyl, thiophenyl, quinolyl, triazolyl, tetrazolyl, isoquinolyl, indolyl in particular pyrrolyl, imidazolyl, pyridinyl, pyrimidinyl, thiophenyl, quinolyl, tetrazolyl, and isoquinolyl

The term "heterocyclyl" is intended to mean a non-aromatic carbocyclic ring or ring system where one or more of the carbon atoms have been replaced with heteroatoms, e.g. nitrogen (=N- or -NH-), sulphur, and/or oxygen atoms. Examples of such heterocyclyl groups are imidazolidine, piperazine, hexahydropyridazine, hexahydropyrimidine, diazepane, diazocane, pyrrolidine, piperidine, azepane, azocane, aziridine, azirine, azetidione, pyrrolidine, tropane, oxazinane (morpholine), azepine, dihydroazepine, tetrahydroazepine, and hexahydroazepine, oxazolane, oxazepane, oxazocane, thiazolane, thiazinane, thiazepane, thiazocane, oxazetane, diazetane, thiazetane, tetrahydrofuran, tetrahydropyran, oxepane, tetrahydrothiophene, tetrahydrothiopyrane, thiepane, dithiane, dithiepane, dioxane, dioxepane, oxathiane, oxathiepane. The most interesting examples are imidazolidine, piperazine, hexahydropyridazine, hexahydropyrimidine, diazepane, diazocane, pyrrolidine, piperidine, azepane, azocane, azetidione, tropane, oxazinane (morpholine), oxazolane, oxazepane, thiazolane, thiazinane, and thiazepane, in particular

imidazolidine, piperazine, hexahydropyridazine, hexahydropyrimidine, diazepane, pyrrolidine, piperidine, azepane, oxazinane (morpholine), and thiazinane

- In the present context, i.e. in connection with the terms "aryl", "heteroaryl", and heterocyclyl, the term "optionally substituted" is intended to mean that the group in question may be substituted one or several times, preferably 1-5 times, in particular 1-3 times) with group(s) selected from hydroxy (which when present in an enol system may be represented in the tautomeric keto form), C₁₋₆-alkyl, C₁₋₆-alkoxy, C₂₋₆-alkenyloxy, oxo (which may be represented in the tautomeric enol form), carboxy, C₁₋₆-alkoxycarbonyl, C₁₋₆-alkylcarbonyl, formyl, aryl, aryloxy, arylamino, aryloxycarbonyl, arylcarbonyl, heteroaryl, heteroarylamino, amino, mono- and di(C₁₋₆-alkyl)amino, carbamoyl, mono- and di(C₁₋₆-alkyl)aminocarbonyl, amino-C₁₋₆-alkyl-aminocarbonyl, mono- and di(C₁₋₆-alkyl)-amino-C₁₋₆-alkyl-aminocarbonyl, C₁₋₆-alkylcarbonylamino, cyano, guanidino, carbamido, C₁₋₆-alkanoyloxy, C₁₋₆-alkyl-sulphonyl-amino, aryl-sulphonyl-amino, heteroaryl-sulphonyl-amino, C₁₋₆-alkyl-sulphonyl, C₁₋₆-alkyl-sulphinyl, C₁₋₆-alkylsulphonyloxy, nitro, sulphanyl, amino, amino-sulfonyl, mono- and di(C₁₋₆-alkyl)amino-sulfonyl, dihalogen-C₁₋₄-alkyl, trihalogen-C₁₋₄-alkyl, halogen, where aryl and heteroaryl representing substituents may be substituted 1-3 times with C₁₋₄-alkyl, C₁₋₄-alkoxy, nitro, cyano, amino or halogen, and any alkyl, alkoxy, and the like representing substituents may be substituted with hydroxy, C₁₋₆-alkoxy, C₂₋₆-alkenyloxy, amino, mono- and di(C₁₋₆-alkyl)amino, carboxy, C₁₋₆-alkylcarbonylamino, halogen, C₁₋₆-alkylthio, C₁₋₆-alkyl-sulphonyl-amino, or guanidine

- Preferably, the substituents are selected from hydroxy, C₁₋₆-alkyl, C₁₋₆-alkoxy, oxo (which may be represented in the tautomeric enol form), carboxy, C₁₋₆-alkylcarbonyl, formyl, amino, mono- and di(C₁₋₆-alkyl)amino, carbamoyl, mono- and di(C₁₋₆-alkyl)aminocarbonyl, amino-C₁₋₆-alkyl-aminocarbonyl, C₁₋₆-alkylcarbonylamino, guanidino, carbamido, C₁₋₆-alkyl-sulphonyl-amino, aryl-sulphonyl-amino, heteroaryl-sulphonyl-amino, C₁₋₆-alkyl-sulphonyl, C₁₋₆-alkyl-sulphinyl, C₁₋₆-alkylsulphonyloxy, sulphanyl, amino, amino-sulfonyl, mono- and di(C₁₋₆-alkyl)amino-sulfonyl or halogen, where any alkyl, alkoxy and the like representing substituents may be substituted with hydroxy, C₁₋₆-alkoxy, C₂₋₆-alkenyloxy, amino, mono- and di(C₁₋₆-alkyl)amino, carboxy, C₁₋₆-alkylcarbonylamino, halogen, C₁₋₆-alkylthio, C₁₋₆-alkyl-sulphonyl-amino, or guanidine. Especially preferred examples are C₁₋₆-alkyl, C₁₋₆-alkoxy, amino, mono- and di(C₁₋₆-alkyl)amino, sulphanyl, carboxy or halogen, where any alkyl, alkoxy and the like representing substituents may be substituted with hydroxy, C₁₋₆-alkoxy, C₂₋₆-alkenyloxy, amino, mono- and di(C₁₋₆-alkyl)amino, carboxy, C₁₋₆-alkylcarbonylamino, halogen, C₁₋₆-alkylthio, C₁₋₆-alkyl-sulphonyl-amino, or guanidine

- In the present context the term "nitrogen-containing heterocyclic ring" is intended to mean heterocyclic ring or ring system in which at least one nitrogen atom is present. Such a nitrogen is, with reference to the formula, carrying the substituents R₁ and R₂. The heterocyclic ring or ring system is a ring or ring system where one or more of the carbon atoms have been replaced with heteroatoms, e.g. nitrogen (=N- or -N-), sulphur, and/or oxygen atoms. Examples of such rings are aromatic rings such as pyridine, pyridazine, pyrimidine, pyrazine, triazine, thiophene, oxazole, isoxazole, thiazole, isothiazole, pyrrole,

imidazole, pyrazole, tetrazole, quinoline, benzothiazole, benzotriazole, benzodiazole, benzoxazole, triazole, isoquinoline, indole, benzopyrazole, thiadiazole, and oxadiazole. The most interesting examples of aromatic rings are pyridine, pyridazine, pyrimidine, pyrazine, thiophene, tetrazole, oxazole, isoxazole, thiazole, isothiazole, pyrrole, imidazole, pyrazole, quinoline, triazole, isoquinoline, and indole, in particular pyridine, thiophene, imidazole, quinoline, isoquinoline, indole, and tetrazole.

Other examples of such rings are non-aromatic rings such as imidazolidine, piperazine, hexahydropyridazine, hexahydropyrimidine, diazepane, diazocane, pyrrolidine, piperidine, azepane, azocane, aziridine, azirine, azetidine, pyrrolidine, tropane, oxazinane (morpholine), azepine, dihydroazepine, tetrahydroazepine, and hexahydroazepine, oxazolane, oxazepane, oxazocane, thiazolane, thiazinane, thiazepane, thiazocane, oxazetane, diazetane, and thiazetane. The most interesting examples of non-aromatic rings are imidazolidine, piperazine, hexahydropyridazine, hexahydropyrimidine, diazepane, diazocane, pyrrolidine, piperidine, azepane, azocane, azetidine, tropane, oxazinane (morpholine), oxazolane, oxazepane, thiazolane, thiazinane, and thiazepane, in particular imidazolidine, piperazine, hexahydropyridazine, hexahydropyrimidine, diazepane, pyrrolidine, piperidine, azepane, oxazinane (morpholine), and thiazinane.

In the present context, i.e. in connection with the term "nitrogen-containing heterocyclic ring", the term "optionally substituted" is intended to mean that the group in question may be substituted one or several times, preferably 1-5 times, in particular 1-3 times) with group(s) selected from the same substituents as defined above for "optionally substituted aryl".

As it will be evident from the formulae defined herein and the definitions associated therewith, there may be one or several asymmetric carbon atoms present in the compounds depending on the nature of the substituents. The compounds are intended to include all stereoisomers arising from the presence of any and all isomers as well as mixtures thereof, including racemic mixtures.

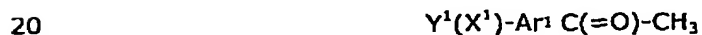
It should furthermore be understood that the compounds defined herein include possible salts thereof, of which pharmaceutically acceptable salts are of course especially relevant for the therapeutic applications. Salts include acid addition salts and basic salts. Examples of acid addition salts are hydrochloride salts, fumarate, oxalate, etc. Examples of basic salts are salts where the (remaining) counter ion is selected from alkali metals, such as sodium and potassium, alkaline earth metals, such as calcium salts, potassium salts, and ammonium ions ($^+N(R')_4$, where the R's independently designates optionally substituted C_{1-6} -alkyl, optionally substituted C_{2-6} -alkenyl, optionally substituted aryl, or optionally substituted heteroaryl). Pharmaceutically acceptable salts are, e.g., those described in Remington's - The Science and Practice of Pharmacy, 20th Ed. Alfonso R Gennaro (Ed.), Lippincott, Williams & Wilkins, ISBN 0683306472, 2000, and in Encyclopedia of Pharmaceutical Technology.

Thus, chalcones with amino groups can be prepared in their salt-forms thereby making the compounds particularly useful for pharmaceutical formulations. The use of appropriate selected salt form can be used to control the dissolution rate in vivo. Furthermore, the different salt forms have different bulk-properties which is of importance for the manufacturing process.

Preparation of compounds

The amino-functional chalcones defined herein may be produced by methods known *per se* for the preparation of chalcones or methods which are analogous to such methods. Examples of excellent methods for preparing compounds of the 1,3-bis-aromatic-prop-2-enone or the 1,3-bis-aromatic-prop-2-ynone types are given in the following. Further examples of methods for the preparation of the compound used according to the present invention are described in WO 95/06628 and WO 93/17671 and in the references cited therein.

Compounds of the general formula I in which V is -CH=CH- can be prepared by reacting a ketone (an acetophenone in the case where Ar¹ is phenyl)



with an aldehyde (a benzaldehyde in the case where Ar² is phenyl)



wherein Ar¹, Ar², X¹, X², Y¹, and Y² refers to the definitions given elsewhere herein.

This reaction, which is a condensation reaction, is suitably carried out under acid or base catalysed conditions. A review of such processes may be found in Nielsen, A T, Houlihan, W J, *Org React* **16**, 1968, p 1-444. In particular the method described by Wattanasin, S and Murphy, S, *Synthesis* (1980) 647 has been found quite successful. The reaction may suitably be carried out in protic organic solvents, such as lower alcohols (e.g. methanol, ethanol, or tert-butanol), or lower carboxylic acids (formic, glacial acetic, or propionic acid), or in aprotic organic solvents such as ethers (e.g. tetrahydrofuran, dioxane, or diethyl ether), liquid amides (e.g. dimethylformamide or hexamethylphosphordiamide), dimethylsulfoxide, or hydrocarbons (e.g. toluene or benzene), or mixtures of such solvents. When carrying out the reaction under base catalysed conditions, the catalyst may be selected from sodium, lithium, potassium, barium, calcium, magnesium, aluminum, ammonium, or quaternary ammonium hydroxides, lower alkoxides (e.g. methoxides, ethoxides, tert-butoxides), carbonates, borates, oxides, hydrides, or amides of lower secondary amines (e.g. diisopropyl amides or methylphenyl amides). Primary aromatic amines such as aniline, free secondary amines such as dimethyl amine, diethyl amine, piperidine, or pyrrolidine as well as basic ion exchange resins may also be used.

Acid catalysts may be selected from hydrogen chloride, hydrogen bromide, hydrogen iodide, sulfuric acid, sulfonic acids (such as paratoluenesulfonic or methanesulfonic acid), lower carboxylic acids (such as formic, acetic or propionic acid), lower halogenated
 5 carboxylic acids (such as trifluoroacetic acid), Lewis acids (such as BF_3 , POCl_3 , PCl_5 , or FeCl_3), or acid ion exchange resins

A drawback of the base catalysed condensation is the poor yield obtained if the aromatic ring in which the ketone or the aldehyde or both is substituted with one or more hydroxy
 10 groups This drawback can be overcome by masking the phenolic group as described by T Hidetsugu et al in EP 0 370 461 Deprotection is easily performed by mineral acids such as hydrochloric acid

The reaction is typically carried out at temperatures in the range of 0-100°C, e g at room
 15 temperature Reaction times are typically from 30 min to 24 hours

The alkyl- or dialkyl aminomethyl-acetophenones and -benzaldehydes were prepared by reductive amination using substituted benzaldehyde, amine and sodium triacetoxymethylborohydride The alkyl- or dialkyl aminoalkyl-acetophenones and -benzaldehydes
 20 were prepared from the corresponding bromo-compounds using halogen/metal exchange ($n\text{-BuLi}$) and quenching with N,N -dimethylacetamide and dimethylformamide, respectively

Compounds of the general formula I in which V is $-\text{C}\equiv\text{C}-$ may be prepared by reacting an activated derivative of a carboxylic acid of the general formula
 25



with an ethyne derivative



wherein Ar^1 , Ar^2 , X^1 , X^2 , Y^1 , and Y^2 refers to the definitions given elsewhere herein

Reactions of this type are described by Tohda, Y, Sonogashihara, K, Haghara, N,
 35 *Synthesis* **1977**, p 777-778 It is contemplated that the activated derivative of the carboxylic acid may be an activated ester, an anhydride or, preferably, an acid halogenide, in particular the acid chloride The reaction is normally carried out using the catalysts described by Tohda, Y et al cited above, namely copper(I)iodide/triphenylphosphine-palladium dichloride The reaction is suitably carried out in triethylamine, a mixture of
 40 triethylamine and pyridine or triethylamine and toluene under a dry inert atmosphere such as nitrogen or argon The reaction is generally carried out at reduced temperature such as in the range from -80°C to room temperature, the reaction time typically being from 30 minutes to 6 hours

In the above reactions, it may be preferred or necessary to protect various sensitive or reactive groups present in the starting materials to prevent said groups from interfering with the reactions. Such protection may be carried out in a well-known manner, e.g. as described in "Protective Groups in Organic Chemistry" by Wuts and Greene, Wiley-

5 Interscience, ISBN 0471160199, 3rd edition (May 15, 1999). For example, in the reaction between the activated acid derivative and the acetylene derivative, a hydroxy group on Ar¹ and/or Ar² may be protected in the form of the methoxymethyl ether, N,N-dimethylcarbamoyl ester, or allyl ether. The protecting group may be removed after the reaction in a manner known *per se*.

10

The ethyne derivative may be prepared by standard methods, e.g. as described by Nielsen, S. F. et al., Bioorg. Med. Chem. 6, pp 937-945 (1998). The carboxylic acids may likewise be prepared by standard procedures or by reductive amination as described in the examples.

15

Compounds of the general formula I in which V is -CH₂-CH₂- can be prepared by ionic hydrogenation of the corresponding α,β -unsaturated compound where V is -CH=CH- as it has been described by the inventors in Nielsen, S. F. et al. Tetrahedron, 53, pp 5573-5580 (1997) and in the examples (see Figure 2).

20

Further possible synthetic routes for the preparation of the saturated variants are described in "Advanced Organic Chemistry" by Jerry March, 3rd ed. (especially chapter 15, pages 691-700) and references cited therein. Thus, it is possible to obtain a large variety of compounds of the 1,3-bis-aromatic-propan-1-one type from the corresponding prop-2-

25 en-1-ones

Medical uses

It has been demonstrated herein (see the Examples section) that the novel compound have interesting properties as bacteriostatic, bacteriocidal and antiparasitic agents. It is of course possible that the compounds also have other interesting properties to be utilised in the medical field.

30

Thus, the present invention provides a compound (chalcone derivative) as defined herein for use as a drug substance.

35

In particular, the chalcone derivative may be used for the treatment of bacterial infections in a mammal in need thereof. Such bacterial infection may be caused by common Gram-positive and Gram-negative pathogens as well as microaerophilic and anaerobic bacteria. As a particularly relevant example of a bacteria against which chalcone derivatives have effect can be mentioned antibiotic-sensitive and -resistant strains of *S. aureus* and *E. faecium*. Other examples common causes of community acquired and nosocomial respiratory infections including *S. pneumoniae*, *S. pyogenes* and members of *Enterobacteriaceae* (e.g. *E. coli*), microaerophilic bacteria associated with gastric disease.

40

(e g *Helicobacter pylori*) and pathogenic anaerobic bacteria (e g *Bacteroides fragilis* and *Clostridium species*)

Also, the chalcone derivatives can be used for the treatment of infections caused by
5 protozoa in a mammal Examples of infections are those caused by a protozoa selected
from *Plasmodium falciparum*, *Plasmodium vivax*, *Plasmodium ovale* and *Plasmodium
malariae*

Furthermore, the chalcone derivatives can be used for the preparation of a pharmaceutical
10 composition for the treatment of infections in a mammal caused by *Leishmania spp* Such
infections may be cutaneous and/or visceral

Preliminary results have shown that compounds wherein the Y¹ is the amino-substituent, in
particular positioned in the 2 or 3 position where Ar¹ is phenyl, are particularly promising
15 for the treatment of infections caused by *Leishmania spp* Those in which X² represents at
least one substituent selected from C₁₋₆-alkyl, C₁₋₆-alkoxy, C₁₋₆-alkylcarbonyl, optionally
substituted aryl, optionally substituted aryloxy, optionally substituted arylamino, optionally
substituted heteroaryl, optionally substituted heteroarylamino, mono- and di(C₁₋₆-
alkyl)amino, C₁₋₆-alkylcarbonylamino, optionally substituted C₁₋₆-alkylthio, optionally
20 substituted heterocyclyl, optionally substituted heterocyclyloxy, optionally substituted
heterocyclylamino and halogen, such as where X² represent the 2,4 or 2,5 substituents of
a phenyl group as Ar², appear to be particularly promising

Other preliminary results indicate that compounds wherein the Y¹ is the amino-substituent,
25 in particular positioned in the 2 position where Ar¹ is phenyl, are particularly promising for
the treatment of infections caused by malaria Those in which X² represents at least one
substituent selected from C₁₋₆-alkyl, C₁₋₆-alkoxy, C₁₋₆-alkylcarbonyl, optionally substituted
aryl, optionally substituted aryloxy, optionally substituted arylamino, optionally substituted
heteroaryl, optionally substituted heteroarylamino, mono- and di(C₁₋₆-alkyl)amino, C₁₋₆-
30 alkylcarbonylamino, optionally substituted C₁₋₆-alkylthio, optionally substituted
heterocyclyl, optionally substituted heterocyclyloxy, optionally substituted
heterocyclylamino and halogen, such as where X² represent the 2,5 substituents of a
phenyl group as Ar², appear to be particularly promising

Still other preliminary results indicate that compounds wherein the Y¹ is the amino-
substituent, in particular positioned in the 2, 3 or 4 position where Ar¹ is phenyl, are
particularly promising for the treatment of infections caused by *S aureus* Those in which
X² represents at least one substituent selected from C₁₋₆-alkyl, C₁₋₆-alkoxy, C₁₋₆-
alkylcarbonyl, optionally substituted aryl, optionally substituted aryloxy, optionally
40 substituted arylamino, optionally substituted heteroaryl, optionally substituted
heteroarylamino, mono- and di(C₁₋₆-alkyl)amino, C₁₋₆-alkylcarbonylamino, optionally
substituted C₁₋₆-alkylthio, optionally substituted heterocyclyl, optionally substituted
heterocyclyloxy, optionally substituted heterocyclylamino and halogen appear to be
particularly promising

The chalcone derivatives are typically formulated in a pharmaceutical composition prior to use as a drug substance

5 Formulation of pharmaceutical compositions

The administration route of the compounds (amino-functional chalcones) as defined herein may be any suitable route which leads to a concentration in the blood or tissue corresponding to a therapeutic concentration. Thus, e.g., the following administration routes may be applicable although the invention is not limited thereto: the oral route, the
10 parenteral route, the cutaneous route, the nasal route, the rectal route, the vaginal route and the ocular route. It should be clear to a person skilled in the art that the administration route is dependant on the particular compound in question, particularly, the choice of administration route depends on the physico-chemical properties of the compound together with the age and weight of the patient and on the particular disease or
15 condition and the severity of the same.

The compounds as defined herein may be contained in any appropriate amount in a pharmaceutical composition, and are generally contained in an amount of about 1-95% by weight of the total weight of the composition. The composition may be presented in a
20 dosage form which is suitable for the oral, parenteral, rectal, cutaneous, nasal, vaginal and/or ocular administration route. Thus, the composition may be in form of, e.g., tablets, capsules, pills, powders, granulates, suspensions, emulsions, solutions, gels including hydrogels, pastes, ointments, creams, plasters, drenches, delivery devices, suppositories, enemas, injectables, implants, sprays, aerosols and in other suitable form.

25 The pharmaceutical compositions may be formulated according to conventional pharmaceutical practice, see, e.g., "Remington's Pharmaceutical Sciences" and "Encyclopedia of Pharmaceutical Technology", edited by Swarbrick, J. & J. C. Boylan, Marcel Dekker, Inc., New York, 1988. Typically, the compounds defined herein are
30 formulated with (at least) a pharmaceutically acceptable carrier or excipient. Pharmaceutically acceptable carriers or excipients are those known by the person skilled in the art.

Thus, the present invention provides a pharmaceutical composition comprising a
35 compound as defined herein in combination with a pharmaceutically acceptable carrier.

Pharmaceutical compositions according to the present invention may be formulated to release the active compound substantially immediately upon administration or at any substantially predetermined time or time period after administration. The latter type of
40 compositions are generally known as controlled release formulations.

In the present context, the term "controlled release formulation" embraces i) formulations which create a substantially constant concentration of the drug within the body over an extended period of time, ii) formulations which after a predetermined lag time create a

- substantially constant concentration of the drug within the body over an extended period of time, iii) formulations which sustain drug action during a predetermined time period by maintaining a relatively, constant, effective drug level in the body with concomitant minimization of undesirable side effects associated with fluctuations in the plasma level of the active drug substance (sawtooth kinetic pattern), iv) formulations which attempt to localize drug action by, e g , spatial placement of a controlled release composition adjacent to or in the diseased tissue or organ, v) formulations which attempt to target drug action by using carriers or chemical derivatives to deliver the drug to a particular target cell type
- 5
- 10 Controlled release formulations may also be denoted "sustained release", "prolonged release", "programmed release", "time release", "rate-controlled" and/or "targeted release" formulations

- Controlled release pharmaceutical compositions may be presented in any suitable dosage forms, especially in dosage forms intended for oral, parenteral, cutaneous nasal, rectal, vaginal and/or ocular administration Examples include single or multiple unit tablet or capsule compositions, oil solutions, suspensions, emulsions, microcapsules, microspheres, nanoparticles, liposomes, delivery devices such as those intended for oral, parenteral, cutaneous, nasal, vaginal or ocular use
- 15

- 20 Preparation of solid dosage forms for oral use, controlled release oral dosage forms, fluid liquid compositions, parenteral compositions, controlled release parenteral compositions, rectal compositions, nasal compositions, percutaneous and topical compositions, controlled release percutaneous and topical compositions, and compositions for administration to the eye can be performed essentially as described in the applicant's earlier International application No WO 99/00114, page 29, line 9, to page 40, line 3 Also, and more generally, the formulation and preparation of the above-mentioned compositions are well-known to those skilled in the art of pharmaceutical formulation Specific formulations can be found in "Remington's Pharmaceutical Sciences"
- 25

30

Dosages

- The compound are preferably administered in an amount of about 0.1-50 mg per kg body weight per day, such as about 0.5-25 mg per kg body weight per day
- 35 For compositions adapted for oral administration for systemic use, the dosage is normally 2 mg to 1 g per dose administered 1-4 times daily for 1 week to 12 months depending on the disease to be treated

- The dosage for oral administration for the treatment of parasitic diseases is normally 1 mg to 1 g per dose administered 1-2 times daily for 1-4 weeks, in particular the treatment of malaria is to be continued for 1-2 weeks whereas the treatment of leishmaniasis will normally be carried out for 3-4 weeks
- 40

The dosage for oral administration for the treatment of bacterial diseases is normally 1 mg to 1 g per dose administered 1-4 times daily for 1 week to 12 months, in particular, the treatment of tuberculosis will normally be carried out for 6-12 months

- 5 The dosage for oral administration of the composition in order to prevent diseases is normally 1 mg to 75 mg per kg body weight per day. The dosage may be administered once or twice daily for a period starting 1 week before the exposure to the disease until 4 weeks after the exposure
- 10 For compositions adapted for rectal use for preventing diseases, a somewhat higher amount of the compound is usually preferred, i.e. from approximately 1 mg to 100 mg per kg body weight per day

- For parenteral administration, a dose of about 0.1 mg to about 50 mg per kg body weight per day is convenient. For intravenous administration a dose of about 0.1 mg to about 20 mg per kg body weight per day administered for 1 day to 3 months is convenient. For intraarticular administration a dose of about 0.1 mg to about 20 mg per kg body weight per day is usually preferable. For parenteral administration in general, a solution in an aqueous medium of 0.5-2% or more of the active ingredients may be employed

- 20 For topical administration on the skin, a dose of about 1 mg to about 5 g administered 1-10 times daily for 1 week to 12 months is usually preferable

- In many cases, it will be preferred to administer the compound defined herein together with another antiparasitic, antimycotic or antibiotic drug, thereby reducing the risk of development of resistance against the conventional drugs, and reducing the amount of each of the drugs to be administered, thus reducing the risk of side effects caused by the conventional drugs. Important aspects of this is the use of the compound against Leishmania, where the compound I is combined with another antileishmanial drug, or the antimalarial use of the compound I where the compound I is used together with another antimalarial drug

Method of prediction

- 35 In a separate aspect, the present invention also provides a method of predicting whether a chemical compound has a potential inhibitory effect against a microorganism selected from *Helicobacter pylori* and *Plasmodium falciparum*, said method comprising preparing a mixture of a dihydroorotate dehydrogenase, a substrate for dihydroorotate dehydrogenase and the chemical compound, measuring the enzymatic activity of dihydroorotate dehydrogenase (A), comparing the enzymatic activity of dihydroorotate dehydrogenase (A) with the standard activity of dihydroorotate dehydrogenase (B) corresponding to the activity of a dihydroorotate dehydrogenase in a similar sample, but without the chemical compound, predicting that the chemical compound has a potential inhibitory effect against *Helicobacter pylori* and *Plasmodium falciparum* if A is significantly lower than B

The method can be performed as described under *DHODH Assay* in the Examples section. It should be noted that the method is not only applicable for the chalcone derivatives defined herein, but can be generally applied to predict the potential inhibitory effect of any compound. Preferably, however, the chemical compound is a chalcone derivative, e.g. a chalcone derivative as defined herein.

EXAMPLES

Preparation of compounds

The general method for the preparation of the A ring or B ring having the amino-functional group is illustrated in Figure 1.

General procedure A

Preparation of alkyl- or dialkyl aminomethyl acetophenones

To a solution of 2-methyl-[1,3]dioxan-2-yl benzaldehyde (165 mmol) and amine (247 mmol) in dry THF (1.5 L) was added sodium triacetoxyborohydride (257 mmol) under argon. The resulting suspension was stirred at room temperature for 18 hr. A solution of sodium hydroxide (2M) was added and stirring was continued for approximately 30 min, before the mixture was acidified using HCl (6M). The mixture was stirred for 1 hr and extracted with diethyl ether, which was discarded. The pH of the aqueous phase was adjusted to 11 – 14 using sodium hydroxide and extracted again with diethyl ether. The latter organic phase, was dried over sodium sulphate, filtered and evaporated to give the title products, which were used without further purification.

General procedure B

Preparation of alkyl- or dialkyl aminomethyl benzaldehydes

To a solution of diethoxymethyl benzaldehyde (16.5 mmol) and amine (24.7 mmol) in dry THF (150 mL) was added sodium triacetoxyborohydride (25.7 mmol) under argon. The resulting suspension was stirred at room temperature for 6-18 hr. A solution of sodium hydroxide (2M) was added and stirring was continued for approximately 30 min, before the mixture was acidified using HCl (6M). The mixture was stirred for 1 hr and extracted with diethyl ether, which was discarded. The pH of the aqueous phase was adjusted to 11 – 14 using sodium hydroxide and extracted again with diethyl ether. The latter organic phase, was dried over sodium sulphate, filtered and evaporated to give the title products, which were used without further purification.

General procedure C**Preparation of biaryl carbaldehydes**

- A solution of Na_2CO_3 (44 mmol) in water (20 mL) was added to a solution of bromobenzaldehyde (14.7 mmol) and arylboronic acid (17.6 mmol) in DME (40 mL). The mixture was flushed with argon for 2 minutes followed by addition of $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$ (310 mg, 3 mol %). The reaction was heated at reflux and left overnight under an atmosphere of argon. The reaction was cooled, 2M Na_2CO_3 was added, and the mixture was extracted with EtOAc (3 x 20 mL). The title products were purified by flash chromatography.

10 General procedure D**Preparation of amino benzaldehydes**

- Bromobenzaldehyde diethyl acetal (40 mmol), amine (48 mmol), $\text{Pd}_2(\text{dba})_3$ (0.2 mmol, 1 mol% Pd), *rac*-BINAP (0.6 mmol) and *t*-BuONa (68 mmol) was stirred in degassed toluene (60 mL) at 80°C for 18 h. The darkbrown mixture was poured into icecold hydrochloric acid (1 M, 200 mL) and stirred vigorously for 2 hours at 25°C. The solution was cooled to 0°C and pH was adjusted to 10 using 6M NaOH(aq) and extracted with Et₂O (4 x 100 mL). The organic phase was dried (K_2CO_3) and the solvent was removed under reduced pressure. The resulting crude oil purified by flash chromatography using 5% Et₃N in EtOAc.

20 Procedure E**Preparation of aminoalkoxy benzaldehydes**

- 60% NaH (36.7 mmol) was added to an ice-cooled stirred solution of hydroxy benzaldehyde (36.7 mmol) in dry toluene (200 mL) and DMSO (1 mL). The reaction mixture was allowed to warm to room temperature. In a separate flask NaOH (110 mmol) was added to a solution of aminoalkyl chloride hydrochloride (110 mmol) in water (50 mL) and the solution was stirred for 5 min, before the aqueous phase was extracted with toluene (3 x 30 mL). The toluene phase was dried (Na_2SO_4) and slowly added to the phenolate solution. The solution was heated at 90°C for 16 h. The reaction mixture was cooled to room temperature and washed with water (3 x 100 mL), 2M NaOH (100 mL) and dried (Na_2SO_4). Evaporation *in vacuo* gave the title compounds, which could be used without further purification.

General procedure F**Preparation of aminochalcones from acetophenones and aldehydes**

- To a solution of an acetophenone (2 mmol) and a benzaldehyde (2 mmol) in 96% EtOH (10 mL) was added NaOH (0.2 mmol), and the mixture was stirred for 3-18 hours at 25

°C The mixture was evaporated on Celite® and the product was isolated by flash chromatography. The aminochalcone was dissolved in MeOH/Et₂O (1:9 v/v, 10 mL) and a solution of fumaric acid or oxalic acid in MeOH/Et₂O (1:9 v/v) was added. The salt was filtered off and recrystallised from MeOH or MeCN. Some aminochalcones did not undergo salt formation, and was isolated as the free base. The purity was >95% determined by HPLC.

General procedure G

Preparation of formylchalcones, substituted in the A-ring

10 A solution of diethoxymethyl-phenyl-ethanone (29 mmol), an benzaldehyde (29 mmol), and NaOH (2.9 mmol) in 96% EtOH (100 mL) was stirred for 18 hours at 25 °C. 6M HCl (10 mL) and Et₂O (50 mL) was added and the solution was stirred for 5 hours at 25 °C. H₂O (50 mL) and the mixture was extracted with Et₂O. The organic phases were pooled, dried over Na₂SO₄, and filtered. Evaporation gave the crude title product, which was
15 purified by flash chromatography or crystallization.

General procedure H

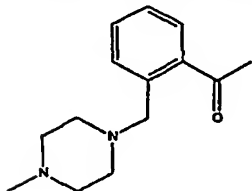
Preparation of formylchalcones, substituted in the B-ring

A solution of diethoxymethyl-benzaldehyde (42 mmol), an acetophenone (42 mmol), and
20 sodium hydroxide (8 mmol) in 96% EtOH (100 mL) was stirred for 18 hours at 25 °C. 6M HCl (10 mL) and Et₂O (50 mL) was added and the solution was stirred for 5 hours at 25 °C. H₂O (50 mL) and the mixture was extracted with Et₂O. The organic phases were pooled, dried over Na₂SO₄, and filtered. Evaporation gave the crude title product, which
25 was purified by flash chromatography or crystallization.

General procedure I

Preparation of aminochalcones from formylchalcones

To a solution of an formylchalcone (3.8 mmol) and amine (5.6 mmol) in dry THF (40 mL) was added sodium triacetoxyborohydride (5.6 mmol) under argon. The resulting
30 suspension was stirred at room temperature for 6-18 hr. A solution of sodium hydroxide (2M) was added and stirring was continued for approximately 30 min, before the mixture extracted with ethyl acetate. The organic phase, was dried over sodium sulphate, filtered, and evaporated on Celite®. The product was isolated by flash chromatography. The purity was >95% determined by HPLC.
35

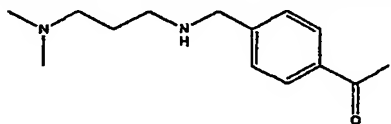
Acetophenones**II-001** 1-[2-(4-Methyl-piperazin-1-ylmethyl)-phenyl]-ethanone

5

General procedure A gave the title product as brown oil in 78% yield

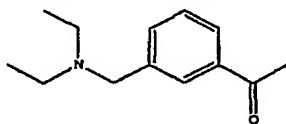
$^1\text{H-NMR}$ (CDCl_3) δ 7.42-7.29 (m, 4H), 3.65 (s, 2H), 2.54 (s, 3H), 2.43 (b, 8H), 2.27 (s, 3H)

10

II-002 1-{4-[(3-Dimethylamino-propylamino)-methyl]-phenyl}-ethanone

General procedure A gave the title product as yellow oil in 18% yield

15 $^1\text{H-NMR}$ (CDCl_3) δ 7.91 (d, 2H), 7.42 (d, 2H), 3.85 (s, 2H), 2.68 (t, 2H), 2.60 (s, 3H), 2.36 (t, 2H), 2.22 (s, 6H), 1.73-1.62 (m, 2H)

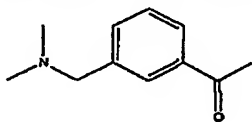
II-003 1-(3-Diethylaminomethyl-phenyl)-ethanone

20

General procedure A gave the title product as yellow oil in 80% yield

$^1\text{H-NMR}$ (CDCl_3) δ 7.91 (s, 1H), 7.82 (d, 1H), 7.57 (d, 1H), 7.40 (t, 1H), 3.61 (s, 2H), 2.61 (s, 3H), 2.52 (t, 4H), 1.04 (t, 6H)

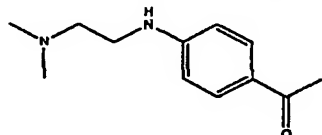
25

II-004 1-(3-Dimethylaminomethyl-phenyl)-ethanone

General procedure A gave the title product as yellow oil in 89% yield

30

$^1\text{H-NMR}$ (CDCl_3) δ 7.89 (s, 1H), 7.85 (d, 1H), 7.52 (d, 1H), 7.42 (t, 1H), 3.47 (s, 2H), 2.61 (s, 3H), 2.25 (s, 6H)

II-005 1-[4-(2-Dimethylamino-ethylamino)-phenyl]-ethanone

5

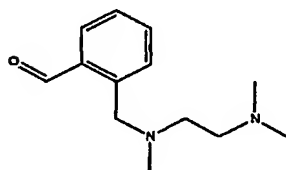
General procedure D gave the title product as brown oil in 86% yield

¹H NMR (CDCl₃) δ 7.76 (d, 2H), 6.50 (d, 2H), 4.90 (bs, 1H), 3.13 (q, 2H), 2.50 (t, 2H), 2.43 (s, 3H), 2.19 (s, 6H)

10

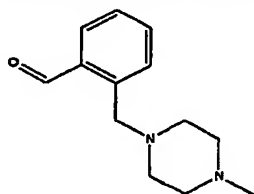
Benzaldehydes**II-006** 2-{[(2-Dimethylamino-ethyl)-methyl-amino]-methyl}-benzaldehyde

15



General procedure B gave the title product as brown oil in 82% yield

¹H-NMR (CDCl₃) δ 10.48 (s, 1H), 7.89 (dd, 1H), 7.53-7.24 (m, 3H), 3.87 (s, 2H), 2.55 (t, 2H), 2.44 (t, 2H), 2.23-2.18 (m, 9H)

II-007 2-(4-Methyl-piperazin-1-ylmethyl)-benzaldehyde

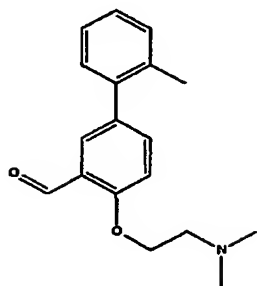
25

General procedure B gave the title product as brown oil in 80% yield

¹H-NMR (300 MHz, CDCl₃) δ 10.41 (s, 1H), 7.87 (d, 1H), 7.51 (dt, 1H), 7.41 (t, 1H), 7.38 (d, 1H), 3.81 (s, 2H), 2.6-2.3 (m, 8H), 2.27 (s, 3H)

30

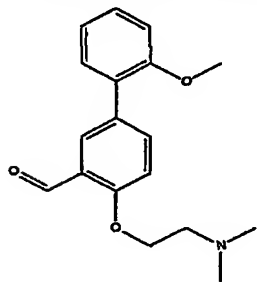
II-008 4-(2-Dimethylamino-ethoxy)-2'-methyl-biphenyl-3-carbaldehyde



General procedure C gave the title compound as white crystals in 79% yield

- 5 $^1\text{H-NMR}$ (300 MHz, CDCl_3) δ 10.56 (s, 1H), 7.82 (d, 1H), 7.51 (dd, 1H), 7.28-7.16 (m, 4H), 7.05 (d, 1H), 4.25 (t, 2H), 2.84 (t, 2H), 2.38 (s, 6H), 2.26 (s, 3H)

II-009 4-(2-Dimethylamino-ethoxy)-2'-methoxy-biphenyl-3-carbaldehyde



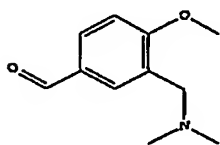
10

General procedure C gave the title compound as light yellow crystals in 78% yield

- $^1\text{H-NMR}$ (300 MHz, DMSO-d_6) δ 10.40 (s, 1H), 7.80-7.72 (m, 2H), 7.38-7.25 (m, 3H), 7.11 (d, 1H), 7.03 (t, 1H), 4.25 (t, 2H), 3.76 (s, 3H), 2.72 (t, 2H), 2.25 (s, 6H)

15

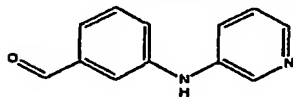
II-010. 3-Dimethylaminomethyl-4-methoxy-benzaldehyde



- 20 To a solution of 4-bromo-2-(dimethylaminomethyl)anisole (12.2 g, 50 mmol) in dry THF (150 mL) at -78°C was added $n\text{-BuLi}$ (2.5 M, 20 mL, 50 mmol) keeping the temperature below -70°C . The orange mixture was stirred for 15 min and dry DMF (4.7 mL, 60 mmol) was added in one portion. The cooling bath was removed and the light yellow mixture was allowed to warm to 20°C . After 30 min the mixture was hydrolysed with 5% Na_2CO_3 (100 mL), and extracted with Et_2O (3 x 100 mL). The organic phase was dried (K_2CO_3) and the solvent was removed under reduced pressure leaving yellow oil (79%) that was pure enough for further reaction.
- 25

¹H-NMR(300 MHz, DMSO-d₆) δ 9.87 (s, 1H), 7.88-7.40 (m, 1H), 7.81 (d, 1H), 7.19 (d, 1H), 3.88 (s, 3H), 3.42 (s, 2H), 2.17 (s, 6H)

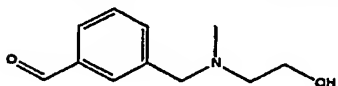
5 **II-011** 3-(Pyridin-3-ylamino)-benzaldehyde



General procedure D gave the title compound as white crystals in 69% yield

10 ¹H-NMR(300 MHz, DMSO-d₆) δ 9.94 (s, 1H), 8.67 (s, 1H), 8.40 (d, 1H), 8.11 (dd, 1H), 7.58-7.50 (m, 2H), 7.47 (d, 1H), 7.43-7.35 (m, 2H), 7.29 (dd, 1H)

II-012 3-[(2-Hydroxy-ethyl)-methyl-amino]-methyl-benzaldehyde



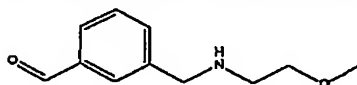
15

General procedure B gave the title product as yellow oil in 84% yield

¹H-NMR (CDCl₃) δ 10.04 (s, 1H), 7.82 (m, 2H), 7.62 (dt, 1H), 7.52 (t, 1H), 3.67 (m, 4H), 2.64 (t, 2H), 2.26 (s, 2H)

20

II-013 3-[(2-Methoxy-ethylamino)-methyl]-benzaldehyde

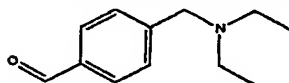


General procedure B gave the title product as yellow oil in 24% yield

25

¹H-NMR (CDCl₃) δ 10.04, (s, 1H), 7.89 (t, 1H), 7.79 (dt, 1H), 7.65 (dt, 1H), 7.51 (t, 1H), 3.92 (s, 2H), 3.55 (t, 2H), 3.39 (s, 3H), 2.84 (t, 2H), 1.79 (s, 1H)

II-014 4-Diethylaminomethyl-benzaldehyde

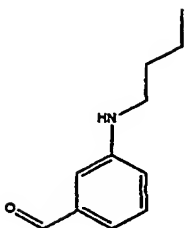


30

General procedure B gave the title product as brown oil in 74% yield

35 ¹H-NMR (CDCl₃) δ 10.02 (s, 1H), 7.85 (d, 2H), 7.55 (d, 2H), 3.66 (s, 2H), 2.56 (k, 4H), 1.07 (t, 6H)

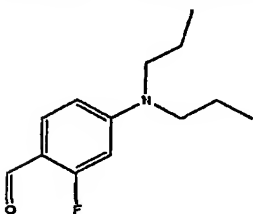
II-015 3-Butylamino-benzaldehyde



General procedure D gave the title compound as yellow oil in 78 % yield

¹H-NMR(300 MHz, DMSO-d₆) δ 9.90 (s, 1H), 7.34 (t, 1H), 7.21 (s, 1H), 7.15-7.05 (m, 2H), 6.96 (dd, 1H), 3.30 (t, 2H), 1.57-1.42 (m, 2H), 1.40-1.25 (m, 2H), 0.92 (t, 3H)

II-016 4-Dibutylamino-2-fluoro-benzaldehyde



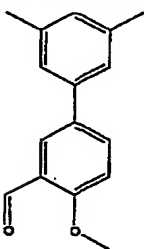
10

General procedure B gave the title product as yellow oil in 56% yield

¹H-NMR (CDCl₃) δ 10.02 (s, 1H), 7.68 (t, 1H), 6.23 (d, 1H), 6.18 (d, 1H), 3.29 (t, 4H), 1.71-1.57 (m, 4H), 0.96 (t, 6H)

15

II-017 4-Methoxy-3',5'-dimethyl-biphenyl-3-carbaldehyde

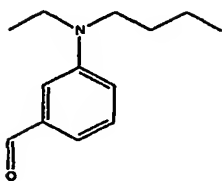


20

General procedure C gave the title compound as white crystals in 81% yield

¹H-NMR(300 MHz, CDCl₃) δ 10.41 (s, 1H), 8.00 (d, 1H), 7.68 (dd, 1H), 7.31 (s, 2H), 7.19 (d, 1H), 6.93 (s, 1H), 4.25 (t, 2H), 2.81 (t, 2H), 2.38 (s, 6H), 2.26 (s, 6H)

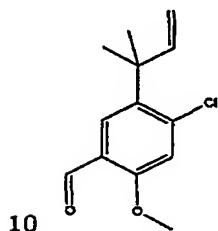
II-018. 3-(Butyl-ethyl-amino)-benzaldehyde



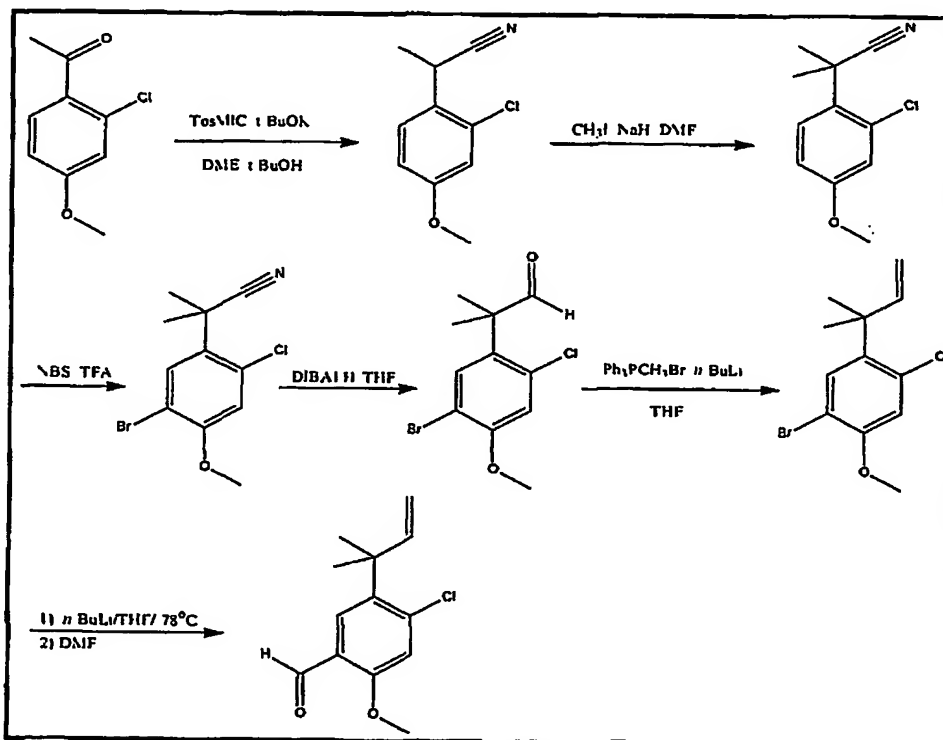
General procedure D gave the title compound as yellow oil in 40 % yield

¹H-NMR(300 MHz, DMSO-d₆) δ 9.90 (s, 1H), 7.35 (t, 1H), 7.12-7.05 (m, 2H), 6.96 (dd, 1H), 3.39 (q, 2H), 3.30 (t, 2H), 1.57-1.42 (m, 2H), 1.40-1.25 (m, 2H), 1.08 (t, 3H), 0.92 (t, 3H)

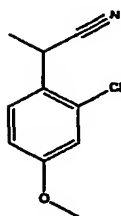
II-019 4-Chloro-5-(1,1-dimethyl-allyl)-2-methoxy-benzaldehyde



10



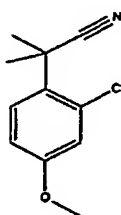
II-020 2-(2-Chloro-4-methoxy-phenyl)propionitrile



A solution of 2'-chloro-4'-methoxyacetophenone (18.5 g, 0.10 mol) and tosylmethylisocyanide (TOSMIC, 21.5 g, 0.11 mol) in dry 1,2-dimethoxyethane (100 mL) was cooled to -10°C. A solution of *t*-BuOK (22.4 g, 0.20 mol) in dry *t*-BuOH (250 mL) was added slowly keeping the temperature below 5°C. The homogeneous orange solution was stirred for 2h/0°C and 1h/25°C. The resulting suspension was evaporated to a slurry. Water (200 mL) was added and extracted with Et₂O (3 x 150 mL). The organic phase was dried (Na₂SO₄) and the solvent was removed under reduced pressure leaving an orange oil. Yield 19 g (97%) GCMS > 98 %

¹H-NMR(300 MHz, DMSO-d₆) δ 7.49 (d, 1H), 7.12 (d, 1H), 7.02 (dd, 1H), 4.42 (q, 1H), 3.80 (s, 3H), 1.55 (d, 3H)

15 **II-021** 2-(2-Chloro-4-methoxy-phenyl)-2-methyl-propionitrile

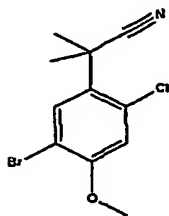


A solution of 2-(2-chloro-4-methoxy-phenyl)propionitrile (19 g, 0.097 mol) and methyl iodide (7 mL, 0.11 mol) in dry DMF (100 mL) was flushed with argon for 2 min and cooled to 0°C. Sodium hydride (60% oil susp, 4.4 g, 0.11 mol) was added in small portions. The thick suspension was stirred for another 18h at 25°C and then poured into water (300 mL) and extracted with Et₂O (3 x 100 mL). The organic phase was dried (Na₂SO₄) and the solvent was removed under reduced pressure leaving a yellow oil which was distilled. Bp 103-106°C/0.06 mbar, clear oil that solidifies on standing. Yield 17.5 g (83%) GCMS > 99%

¹H-NMR(300 MHz, DMSO-d₆) δ 7.43 (d, 1H), 7.13 (d, 1H), 6.98 (dd, 1H), 3.80 (s, 3H), 1.77 (s, 6H)

30

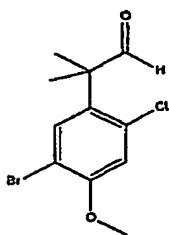
II-022 2-(5-Bromo-2-chloro-4-methoxy-phenyl)-2-methyl-propionitrile



A solution of 2-(2-chloro-4-methoxy-phenyl)-2-methyl-propionitrile (17.5 g, 0.0835 mol) in TFA (100 mL) was cooled to 0°C. N-bromosuccinimide (14.9 g, 0.0835 mol) was added in small portions keeping the temperature below 5°C. The orange solution was stirred for 2 h/25°C and evaporated to dryness. Water (200 mL) was added and the mixture was stirred vigorously for 1 h. The crude product was filtered off and recrystallized from boiling MeOH. The pure product was isolated as white needles. Yield: 13 g (54%). GCMS > 99%.

¹H-NMR(300 MHz, DMSO-d₆) δ 7.56 (s, 1H), 7.23 (s, 1H), 3.84 (s, 3H), 1.70 (s, 6H)

II-023 2-(5-Bromo-2-chloro-4-methoxy-phenyl)-2-methyl-propionaldehyde

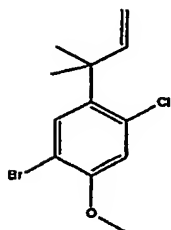


15

A solution of 2-(5-bromo-2-chloro-4-methoxy-phenyl)-2-methyl-propionitrile (13 g, 0.045 mol) in dry THF (80 mL) was cooled to -10°C under argon. DIBALH (1M in THF, 100 mL, 0.10 mol) was added keeping the temperature below 0°C. The mixture was stirred for 30 min/0°C and then 2 h/25°C. The clear solution was carefully poured into icecold hydrochloric acid (2M, 100 mL). The THF was removed under reduced pressure. The aqueous phase was cooled and the crude product was filtered off and recrystallized from boiling MeOH. Yield: 7.8 g (59%). GCMS > 99%.

¹H-NMR(300 MHz, DMSO-d₆) δ 9.61 (s, 1H), 7.68 (s, 1H), 7.27 (s, 1H), 3.89 (s, 3H), 1.40 (s, 6H)

II-024 1-Bromo-4-chloro-5-(1,1-dimethyl-allyl)-2-methoxy-benzene

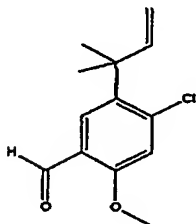


- A suspension of methyltriphenylphosphonium bromide (11.4 g, 0.032 mol) in dry THF (100 mL) was cooled to 0°C under argon. *n*-BuLi (2.5M, 12 mL, 0.030 mol) was added slowly.
- 5 The suspension became more homogenous. The resulting clear orange solution of the ylide was stirred for another 15 min at 0°C. 2-(5-Bromo-2-chloro-4-methoxyphenyl)-2-methylpropionaldehyde (7.8 g, 0.027 mol) was dissolved in dry THF (50 mL) and added to ylide-solution. The mixture was stirred for 3h/25°C and the resulting suspension was quenched with MeOH (10 mL). The solvent was removed under reduced pressure and the crude
- 10 product was purified by flash chromatography using *n*-heptane as eluent. Yield: 3.92 g (50%). GCMS > 99%.

¹H-NMR(300 MHz, DMSO-*d*₆) δ 7.55 (s, 1H), 7.14 (s, 1H), 6.05 (dd, 1H), 5.04 (dd, 1H), 4.92 (dd, 1H), 3.87 (s, 3H), 1.45 (s, 6H).

15

II-019 4-Chloro-5-(1,1-dimethyl-allyl)-2-methoxy-benzaldehyde

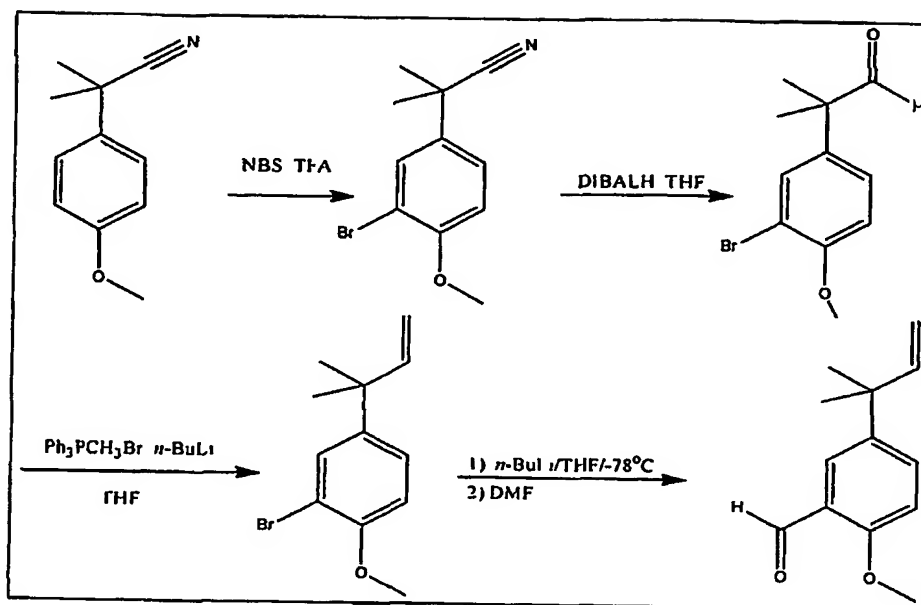
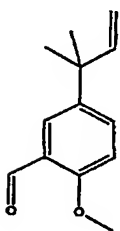


- 20 To a solution of 1-bromo-4-chloro-5-(1,1-dimethyl-allyl)-2-methoxy-benzene (3.92 g, 0.0135 mol) in dry THF (30 mL) was cooled to -78°C under argon. *n*-BuLi (2.5M, 6 mL, 0.0145 mol) was added keeping the temperature below -70°C. The yellow mixture was stirred for another 15 min and quenched with dry DMF (1.2 mL, 0.015 mol). The cooling bath was removed and the mixture was allowed to warm to 25°C. A saturated solution of
- 25 NaHCO₃ (30 mL) was added and then extracted with EtOAc (3 x 50 mL). The organic phase was dried (Na₂SO₄) and evaporated to dryness. The crude product was recrystallized from MeOH. Yield: 3.00 g (93%). GCMS > 99%.

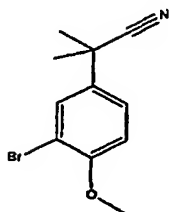
¹H-NMR(300 MHz, DMSO-*d*₆) δ 10.30 (s, 1H), 7.80 (s, 1H), 7.30 (s, 1H), 6.08 (dd, 1H), 5.06 (dd, 1H), 4.91 (dd, 1H), 3.93 (s, 3H), 1.49 (s, 6H).

30

II-025 5-(1,1-Dimethyl-allyl)-2-methoxy-benzaldehyde

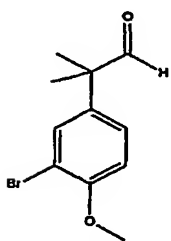


5

II-026 2-(3-Bromo-4-methoxy-phenyl)-2-methyl-propionitrile

- 10 A solution of 2-(4-methoxy-phenyl)-2-methyl-propionitrile (17.5 g, 0.10 mol) in TFA (80 mL) was cooled to 0°C. N-bromosuccinimide (17.8 g, 0.10 mol) was added in small portions keeping the temperature below 5°C. The orange solution was stirred for 2 h/25°C and evaporated to dryness. Water (200 mL) was added and the mixture was stirred vigorously for 1 h. The crude product was filtered off and recrystallized from boiling MeOH.
- 15 The pure product was isolated as white needles. Yield: 19.3 g (76%). GCMS > 99%.

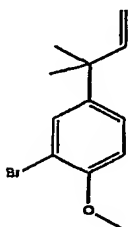
¹H-NMR(300 MHz, DMSO-d₆) δ 7.68 (d, 1H), 7.50 (dd, 1H), 7.16 (d, 1H), 3.86 (s, 3H), 1.70 (s, 6H).

II-027 2-(3-Bromo-4-methoxy-phenyl)-2-methyl-propionaldehyde

- 5 A solution of 2-(3-bromo-4-methoxy-phenyl)-2-methyl-propionitrile (12.71 g, 0.050 mol) in dry THF (100 mL) was cooled to -10°C under argon. DIBALH (1M in THF, 100 mL, 0.10 mol) was added keeping the temperature below 0°C . The mixture was stirred for 30 min/ 0°C and then 2 h/ 25°C . The clear solution was carefully poured into icecold hydrochloric acid (2M, 100 mL). The THF was removed under reduced pressure to give clear oil. The oil was distilled (b.p. $114-130^{\circ}\text{C}/4.3 \times 10^{-3}$ mbar). Yield 7.40 g (58%). GCMS > 99%.

$^1\text{H-NMR}$ (300 MHz, CDCl_3) δ 9.44 (s, 1H), 7.45 (d, 1H), 7.15 (dd, 1H), 6.90 (d, 1H), 3.89 (s, 3H), 1.43 (s, 6H).

15

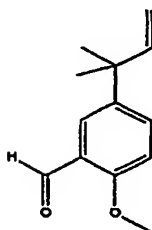
II-028 2-Bromo-4-(1,1-dimethyl-allyl)-1-methoxy-benzene

- 20 A suspension of methyltriphenylphosphonium bromide (7.71 g, 0.0215 mol) in dry THF (100 mL) was cooled to 0°C under argon. *n*-BuLi (2.5M, 8 mL, 0.020 mol) was added slowly. The resulting clear orange solution of the ylide was stirred for another 15 min at 0°C . 2-(3-bromo-4-methoxy-phenyl)-2-methyl-propionaldehyde (3.7 g, 0.014 mol) was dissolved in dry THF (50 mL) and added to ylide-solution. The mixture was stirred for 3 h/ 25°C and the resulting suspension was quenched with MeOH (10 mL). The solvent was removed under reduced pressure and the crude product was purified by flash chromatography using *n*-heptane as eluent. Yield 3.1 g (84%). GCMS > 99%.

$^1\text{H-NMR}$ (300 MHz, CDCl_3) δ 7.50 (d, 1H), 7.23 (dd, 1H), 6.83 (d, 1H), 5.97 (dd, 1H), 5.06 (dd, 1H), 5.02 (dd, 1H), 3.87 (s, 3H), 1.44 (s, 6H).

30

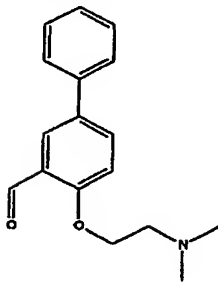
II-025. 5-(1,1-Dimethyl-allyl)-2-methoxy-benzaldehyde



To a solution of 2-Bromo-4-(1,1-dimethyl-allyl)-1-methoxy-benzene (3.1 g, 0.012 mol) in dry THF (50 mL) was cooled to -78°C under argon. *n*-BuLi (2.5M, 5.1 mL, 0.0128 mol) was added keeping the temperature below -70°C . The yellow mixture was stirred for another 15 min and quenched with dry DMF (1.4 mL, 0.018 mol). The cooling bath was removed and the mixture was allowed to warm to 25°C . A saturated solution of NaHCO_3 (30 mL) was added and then extracted with EtOAc (3 x 50 mL). The organic phase was dried (Na_2SO_4) and evaporated to yellow oil. Yield: 2.31 g (94%).

$^1\text{H-NMR}$ (300 MHz, CDCl_3) δ 10.48 (s, 1H), 7.84 (d, 1H), 7.55 (dd, 1H), 6.94 (d, 1H), 6.00 (dd, 1H), 5.05 (dd, 1H), 5.01 (dd, 1H), 3.93 (s, 3H), 1.41 (s, 6H).

II-029 4-(2-Dimethylamino-ethoxy)-biphenyl-3-carbaldehyde



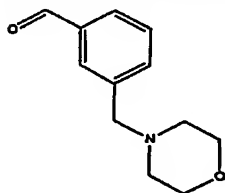
15

General procedure C gave the title product as yellow crystals in 57% yield.

$^1\text{H NMR}$ (CDCl_3) δ 10.48 (s, 1H), 8.01 (d, 1H), 7.71 (dd, 1H), 7.49 (d, 1H), 7.36 (t, 2H), 7.26 (t, 1H), 7.00 (d, 1H), 4.18 (t, 2H), 2.77 (t, 2H), 2.31 (s, 6H).

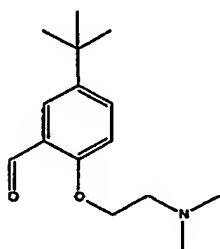
20

II-030 3-Morpholin-4-ylmethyl-benzaldehyde



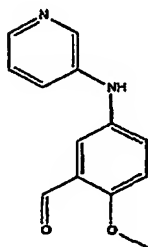
25 General procedure B gave the title product as yellow oil in 71% yield.

$^1\text{H-NMR}$ (CDCl_3) δ 10.05 (s, 1H), 7.88 (s, 1H), 7.81 (d, 1H), 7.64 (d, 1H), 7.51 (t, 1H), 3.74 (t, 4H), 3.58 (s, 2H), 2.48 (t, 4H).

II-031 5-*tert*-Butyl-2-(2-dimethylamino-ethoxy)-benzaldehyde

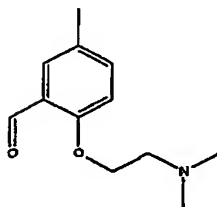
5 General procedure E gave the title product as yellow oil in 93% yield

¹H NMR (CDCl₃) δ 10.50 (s, 1H), 7.85 (d, 1H), 7.57 (dd, 1H), 6.93 (d, 1H), 4.18 (t, 2H), 2.79 (t, 2H), 2.36 (s, 6H), 1.31 (s, 9H)

10 II-032 2-Methoxy-5-(pyridin-3-ylamino)-benzaldehyde

General procedure D gave the title product as yellow oil that precipitated on standing in
15 39% yield

¹H NMR (CDCl₃) δ 10.42 (s, 1H), 8.27 (d, 1H), 8.08 (dd, 1H), 7.55 (d, 1H), 7.33 (dd, 1H), 7.26 (ddd, 1H), 7.11 (dd, 1H), 6.95 (d, 1H), 6.34 (bs, 1H), 3.90 (s, 3H)

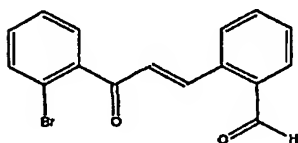
20 II-033 2-(2-Dimethylamino-ethoxy)-5-methyl-benzaldehyde

General procedure E gave the title product as yellow oil in 95% yield
25

¹H NMR (CDCl₃) δ 10.48 (s, 1H), 7.63 (d, 1H), 7.34 (dd, 1H), 6.89 (d, 1H), 4.16 (t, 2H), 2.79 (t, 2H), 2.35 (s, 6H), 2.31 (s, 3H)

Formylchalcones**II-034** (E)-2-[3-(2-Bromo-phenyl)-3-oxo-propenyl]-benzaldehyde

5

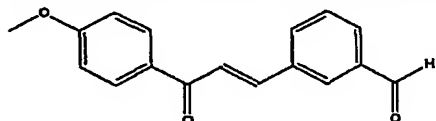


General procedure H gave the title product as yellow crystals in 47% yield

10 ¹H-NMR (CDCl₃) δ 10.21 (s, 1H), 8.24 (d, 1H), 7.86 (dd, 1H), 7.73 (dd, 1H), 7.67-7.57 (m, 3H), 7.50 (dd, 1H), 7.45 (td, 1H), 7.35 (td, 1H), 7.00 (d, 1H)

II-035 (E)-3-[3-(4-Methoxy-phenyl)-3-oxo-propenyl]-benzaldehyde

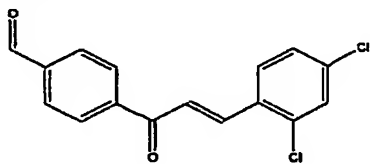
15



General procedure H gave the title compound as white crystals in 53% yield

¹H NMR (300 MHz, CDCl₃) δ 10.08 (s, 1H), 8.42 (bs, 1H), 8.2 (m, 3H), 8.07 (d, 1H), 7.88 (dt, 1H), 7.78 (d, 1H), 7.69 (t, 1H), 7.11 (d, 2H), 3.88 (s, 3H)

20

II-036 (E)-4-[3-(2,4-Dichloro-phenyl)-acryloyl]-benzaldehyde

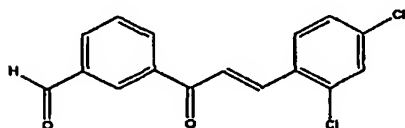
General procedure G gave the title compound as white crystals in 7% yield

25

¹H NMR (300 MHz, CDCl₃) δ 10.13 (s, 1H), 8.15 (m, 3H), 8.02 (d, 2H), 7.70 (d, 1H), 7.49 (d, 1H), 7.46 (d, 1H), 7.33 (dd, 1H)

II-037 (E)-3-[3-(2,4-Dichloro-phenyl)-acryloyl]-benzaldehyde

30



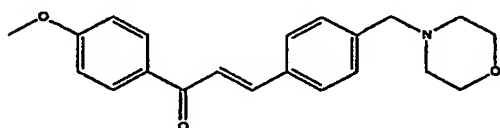
General procedure G gave the title products as a white solid in 7 % yield

¹H-NMR(300 MHz, CDCl₃) δ 10.12 (s, 1H), 8.5 (t, 1H), 8.32-8.26 (m, 1H), 8.18 (d, 1H),
5 8.15-8.10 (m, 1H), 7.72 (d, 1H), 7.72 (s, 1H), 7.54-7.48 (m, 2H), 7.36-7.30 (m, 1H)

Aminochalcones

II-038 (E)- 1-(4-Methoxy-phenyl)-3-(4-morpholin-4-ylmethyl-phenyl)-propenone

10



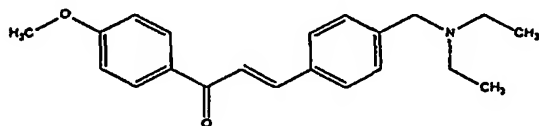
fumarate

General procedure I gave the title compound as slightly yellow crystals in 16% yield

15 ¹H-NMR(300 MHz, DMSO-d₆) δ 8.15 (d, 2H), 7.91 (d, 1H), 7.83 (d, 2H), 7.69 (d, 1H),
7.39 (d, 2H), 7.08 (d, 2H), 6.63 (s, 2H), 3.86 (s, 3H), 3.59 (t, 4H), 3.52 (s, 2H), 2.40 (t,
4H)

II-039 (E)- 3-(4-Diethylaminomethyl-phenyl)-1-(4-methoxy-phenyl)-propenone

20



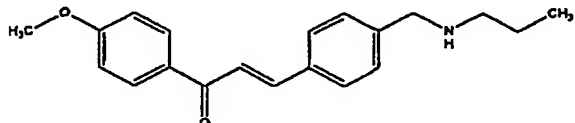
fumarate

General procedure I gave the title compound as slightly yellow crystals in 25% yield

25 ¹H-NMR(300 MHz, DMSO-d₆) δ 8.16 (d, 2H), 7.92 (d, 1H), 7.84 (d, 2H), 7.69 (d, 1H),
7.43 (d, 2H), 7.09 (d, 2H), 6.59 (s, 2H), 3.88 (s, 3H), 3.75 (s, 2H), 2.61 (q, 4H), 1.05 (t,
6H)

II-040 (E)- 1-(4-Methoxy-phenyl)-3-(4-propylaminomethyl-phenyl)-propenone

30

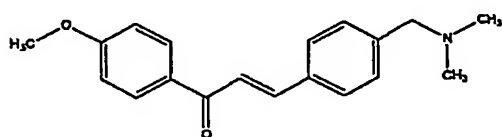


fumarate

General procedure I gave the title compound as white crystals in 59% yield

¹H-NMR(300 MHz, DMSO-d₆) δ 8.17 (d, 2H), 7.95 (d, 1H), 7.88 (d, 2H), 7.70 (d, 1H), 7.51 (d, 2H), 7.09 (d, 2H), 6.51 (s, 2H), 3.96 (s, 2H), 3.87 (s, 3H), 2.70-2.61 (m, 2H), 1.60-1.49 (m, 2H), 0.88 (s, 3H)

5 **II-041** (*E*)-3-(4-Dimethylaminomethyl-phenyl)-1-(4-methoxy-phenyl)-propenone



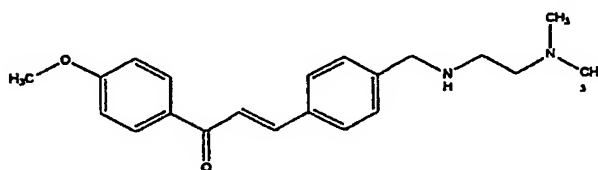
fumarate

General procedure I gave the title compound as off-white crystals in 60% yield

10

¹H-NMR(300 MHz, DMSO-d₆) δ 8.16 (d, 2H), 7.93 (d, 1H), 7.83 (d, 2H), 7.70 (d, 1H), 7.41 (d, 2H), 7.09 (d, 2H), 6.59 (s, 2H), 3.88 (s, 3H), 3.60 (s, 2H), 2.28 (s, 6H)

15 **II-042** (*E*)-3-{4-[(2-Dimethylamino-ethylamino)-methyl]-phenyl}-1-(4-methoxy-phenyl)-propenone



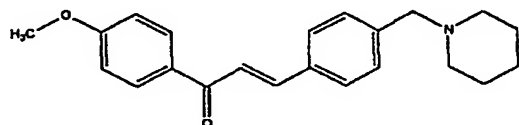
fumarate

General procedure I gave the title compound as white crystals in 27% yield

20

¹H-NMR(300 MHz, DMSO-d₆) δ 8.17 (d, 2H), 7.94 (d, 1H), 7.86 (d, 2H), 7.70 (d, 1H), 7.48 (d, 2H), 7.09 (d, 2H), 6.53 (s, 2H), 3.90 (s, 2H), 3.88 (s, 3H), 2.79 (t, 2H), 2.63 (t, 2H), 2.31 (s, 6H)

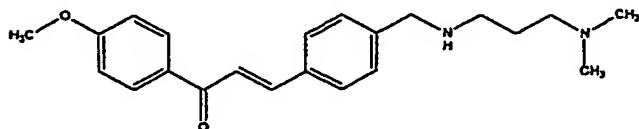
25 **II-043** (*E*)-1-(4-Methoxy-phenyl)-3-(4-piperidin-1-ylmethyl-phenyl)-propenone



General procedure I gave the title compound as yellow crystals in 79% yield

30

¹H-NMR(300 MHz, CDCl₃) δ 8.04 (d, 2H), 7.90 (d, 1H), 7.58 (d, 2H), 7.52 (d, 1H), 7.37 (d, 2H), 6.98 (d, 2H), 3.87 (s, 3H), 3.50 (s, 2H), 2.39 (br, 4H), 1.62-1.52 (m, 4H), 1.49-1.40 (m, 2H)

II-044 (*E*)- 3-{4-[(3-Dimethylamino-propylamino)-methyl]-phenyl}-1-(4-methoxy-phenyl)-propenone

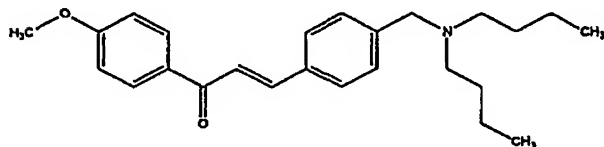
fumarate

5

General procedure I gave the title compound as off-white crystals in 23% yield

¹H-NMR(300 MHz, DMSO-d₆) δ 8.17 (d, 2H), 7.94 (d, 1H), 7.87 (d, 2H), 7.70 (d, 1H), 7.49 (d, 2H), 7.09 (d, 2H), 6.49 (s, 2H), 3.92 (s, 2H), 3.88 (s, 3H), 2.71 (t, 2H), 2.46 (t, 2H), 2.23 (s, 6H), 1.88-1.65 (m, 2H)

10

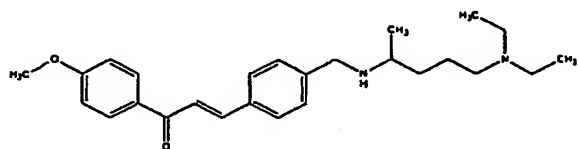
II-045 (*E*)- 3-(4-Dibutylaminomethyl-phenyl)-1-(4-methoxy-phenyl)-propenone

15

General procedure I gave the title compound as yellow crystals in 62% yield

¹H-NMR(300 MHz, CDCl₃) δ 8.04 (d, 2H), 7.80 (d, 1H), 7.58 (d, 2H), 7.52 (d, 1H), 7.38 (d, 2H), 6.98 (d, 2H), 3.90 (s, 3H), 3.57 (s, 2H), 2.40 (t, 4H), 1.49-1.40 (m, 4H), 1.36-1.20 (m, 4H), 0.88 (t, 6H)

20

II-046 (*E*)- 3-{4-[(4-Diethylamino-1-methyl-butylamino)-methyl]-phenyl}-1-(4-methoxy-phenyl)-propenone

25

General procedure I gave the title compound as brown oil in 24% yield

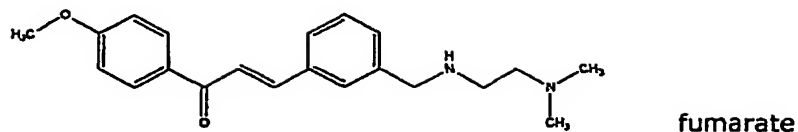
¹H-NMR(300 MHz, CDCl₃) δ 8.04 (d, 2H), 7.80 (d, 1H), 7.59 (d, 2H), 7.52 (d, 1H), 7.38 (d, 2H), 6.98 (d, 2H), 3.90 (s, 3H), 3.57 (s, 2H), 2.79-2.61 (m, 1H), 2.60-2.50 (q, 4H), 2.49-2.40 (t, 2H), 1.52-1.48 (m, 2H), 1.38-1.23 (m, 2H), 1.06 (d, 3H), 1.01 (t, 6H)

30

II-047 (*E*)- 3-{3-[(2-Dimethylamino-ethylamino)-methyl]-phenyl}-1-(4-methoxy-phenyl)-propenone

35

38

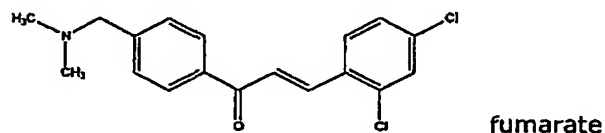


General procedure I gave the title compound as white crystals in 43% yield

- 5 $^1\text{H-NMR}$ (300 MHz, DMSO-d_6) δ 8.16 (d, 2H), 7.95 (s, 1H), 7.93 (d, 1H), 7.81 (d, 1H), 7.70 (d, 1H), 7.52-7.43 (m, 2H), 7.10 (d, 2H), 6.58 (s, 2H), 3.95 (s, 2H), 3.88 (s, 3H), 2.85 (t, 2H), 2.70 (t, 2H), 2.35 (s, 6H)

II-048 (E)- 3-(2,4-Dichloro-phenyl)-1-(4-dimethylaminomethyl-phenyl)-propenone

10

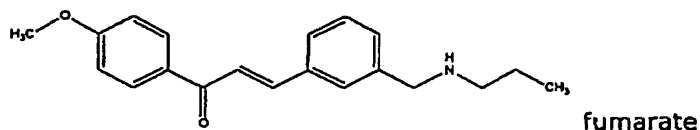


General procedure I gave the title compound as off-white crystals in 72% yield

- 15 $^1\text{H-NMR}$ (300 MHz, DMSO-d_6) δ 8.26 (d, 1H), 8.15 (d, 2H), 8.04 (d, 1H), 7.96 (d, 1H), 7.78 (d, 1H), 7.56 (dd, 1H), 7.52 (d, 2H), 6.60 (s, 2H), 3.60 (s, 2H), 2.22 (s, 6H)

II-049 (E)- 1-(4-Methoxy-phenyl)-3-(3-propylaminomethyl-phenyl)-propenone

20

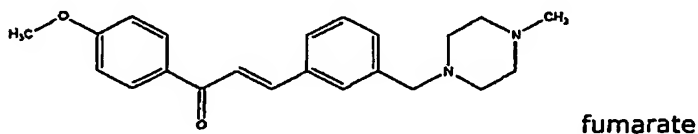


General procedure I gave the title compound as white crystals in 28% yield

- $^1\text{H-NMR}$ (300 MHz, DMSO-d_6) δ 8.15 (d, 2H), 7.98 (s, 1H), 7.94 (d, 1H), 7.80 (d, 1H), 7.69 (d, 1H), 7.52-7.43 (m, 2H), 7.10 (d, 2H), 6.52 (s, 2H), 3.99 (s, 2H), 3.86 (s, 3H), 2.69 (t, 2H), 1.62-1.50 (m, 2H), 0.89 (t, 3H)

II-050 (E)- 1-(4-Methoxy-phenyl)-3-[3-(4-methyl-piperazin-1-ylmethyl)-phenyl]-propenone

30

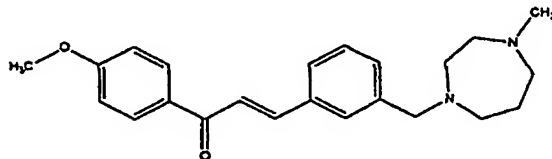


General procedure I gave the title compound as off-white crystals in 43% yield

¹H-NMR(300 MHz, DMSO-d₆) δ 8.16 (d, 2H), 7.92 (d, 1H), 7.80-7.75 (m, 2H), 7.69 (d, 1H), 7.45-7.37 (m, 2H), 6.99 (d, 2H), 6.59 (s, 2H), 3.87 (s, 3H), 3.55 (s, 2H), 2.70-2.55 (br, 4H), 2.54-2.45 (br, 4H), 2.35 (s, 3H)

5

II-051 (*E*)- 1-(4-Methoxy-phenyl)-3-[3-(4-methyl-[1,4]diazepan-1-ylmethyl)-phenyl]-propenone



fumarate

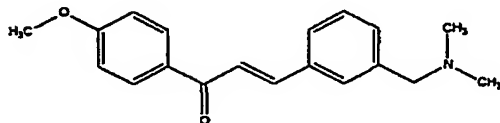
10

General procedure I gave the title compound as off-white crystals in 70% yield

¹H-NMR(300 MHz, DMSO-d₆) δ 8.16 (d, 2H), 7.92 (d, 1H), 7.80-7.75 (m, 2H), 7.70 (d, 1H), 7.45-7.40 (m, 2H), 7.09 (d, 2H), 6.57 (s, 2H), 3.87 (s, 3H), 3.69 (s, 2H), 3.08-3.00 (m, 2H), 2.99-2.97 (m, 2H), 2.80-2.75 (m, 2H), 2.72-2.65 (m, 2H), 2.58 (s, 3H), 1.90-1.81 (m, 2H)

15

II-052 (*E*)- 3-(3-Dimethylaminomethyl-phenyl)-1-(4-methoxy-phenyl)-propenone



20

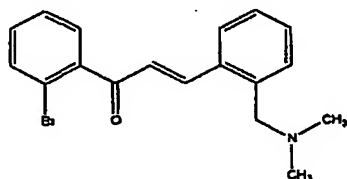
fumarate

General procedure I gave the title compound as white crystals in 23% yield

¹H-NMR(300 MHz, DMSO-d₆) δ 8.16 (d, 2H), 7.92 (d, 1H), 7.80-7.75 (m, 2H), 7.69 (d, 1H), 7.45-7.37 (m, 2H), 7.09 (d, 2H), 6.60 (s, 2H), 3.87 (s, 3H), 3.51 (s, 2H), 2.21 (s, 6H)

25

II-053 (*E*)- 1-(2-Bromo-phenyl)-3-(2-dimethylaminomethyl-phenyl)-propenone

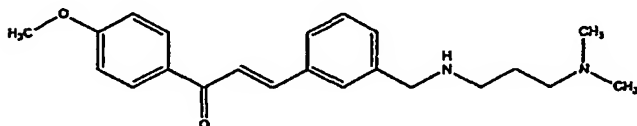


30

General procedure I gave the title compound as slightly green crystals in 17% yield

¹H-NMR(300 MHz, CDCl₃) δ 7.96 (d, 1H), 7.72-7.67 (m, 1H), 7.64 (dd, 1H), 7.44-7.37 (m, 2H), 7.36-7.29 (m, 3H), 7.25-7.21 (m, 1H), 6.95 (d, 1H), 3.35 (s, 2H), 2.07 (s, 6H)

II-054 (E)- 3-{3-[(3-Dimethylamino-propylamino)-methyl]-phenyl}-1-(4-methoxy-phenyl)-propenone

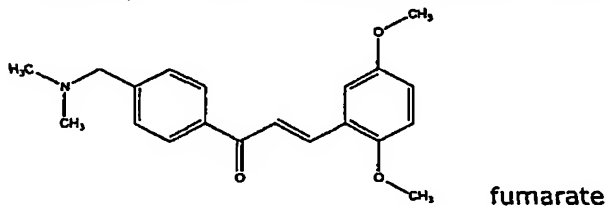


General procedure I gave the title compound as yellow oil in 27% yield

10

¹H-NMR(300 MHz, CDCl₃) δ 8.06 (d, 2H), 7.80 (d, 1H), 7.65-7.50 (m, 3H), 7.40-7.37 (m, 2H), 6.99 (d, 2H), 3.90 (s, 3H), 3.84 (s, 2H), 2.70 (t, 2H), 2.35 (t, 2H), 2.20 (s, 6H), 1.70-1.60 (m, 2H)

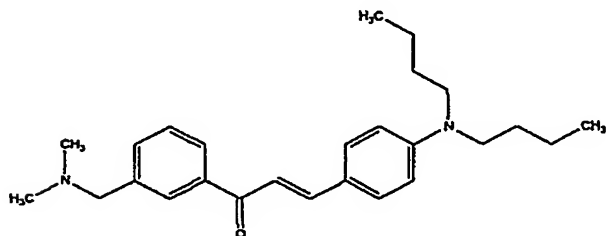
II-055 (E)- 3-(2,5-Dimethoxy-phenyl)-1-(4-dimethylaminomethyl-phenyl)-propenone



General procedure F gave the title compound as yellow crystals in 64% yield

¹H-NMR(300 MHz, DMSO-d₆) δ 7.99 (d, 2H), 7.90 (d, 1H), 7.78 (d, 1H), 7.45-7.30 (m, 3H), 6.90 (s, 2H), 6.45 (s, 2H), 3.70 (s, 2H), 3.65 (s, 3H), 3.45 (s, 3H), 2.21 (s, 6H)

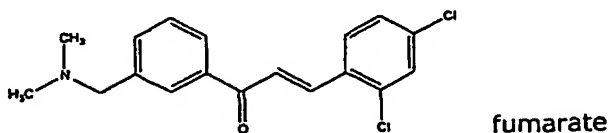
II-056 (E)- 3-(4-Dibutylamino-phenyl)-1-(3-dimethylaminomethyl-phenyl)-propenone



25

General procedure F gave the title compound as orange oil in 24% yield

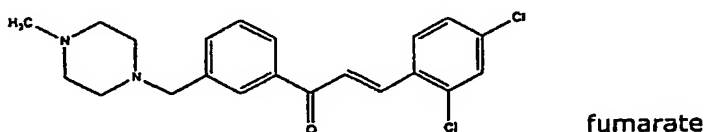
¹H-NMR(300 MHz, CDCl₃) δ 7.91 (d, 2H), 7.84 (d, 1H), 7.75-7.41 (m, 4H), 7.32 (d, 1H), 6.62 (d, 2H), 3.58 (s, 2H), 3.32 (t, 4H), 2.26 (s, 6H), 1.64-1.54 (m, 4H), 1.46-2.9 (m, 4H), 0.97 (t, 6H)

II-057 (E)- 3-(2,4-Dichloro-phenyl)-1-(3-dimethylaminomethyl-phenyl)-propenone

5 General procedure I gave the title compound as white powder in 29% yield

¹H-NMR(300 MHz, DMSO-d₆) δ 8.27 (d, 1H), 8.15-8.07 (m, 2H), 8.02 (d, 1H), 7.95 (d, 1H), 7.77 (d, 1H), 7.65 (d, 1H), 7.60-7.52 (m, 2H), 6.60 (s, 2H), 3.65 (s, 2H), 2.28 (s, 6H)

10

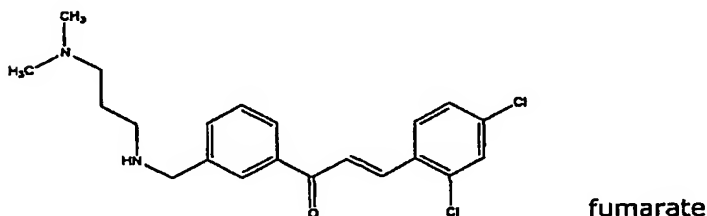
II-058 (E)- 3-(2,4-Dichloro-phenyl)-1-[3-(4-methyl-piperazin-1-ylmethyl)-phenyl]-propenone

15

General procedure I gave the title compound as white powder in 33% yield

¹H-NMR(300 MHz, DMSO-d₆) δ 8.04 (d, 1H), 7.87 (d, 1H), 7.84-7.69 (m, 3H), 7.55 (d, 1H), 7.43-7.29 (m, 3H), 6.60 (s, 4H), 3.61 (s, 2H), 2.70-2.55 (br, 4H), 2.50-2.40 (br, 4H), 2.35 (s, 3H)

20

II-059 (E)- 3-(2,4-Dichloro-phenyl)-1-{3-[(3-dimethylamino-propylamino)-methyl]-phenyl}-propenone

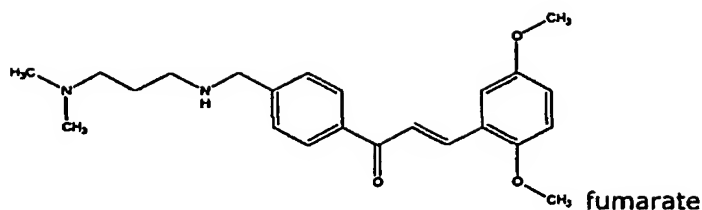
25

General procedure I gave the title compound as white powder in 8% yield

¹H-NMR(300 MHz, DMSO-d₆) δ 8.26-8.23 (m, 2H), 8.13 (br d, 1H), 8.03 (d, 1H), 7.96 (d, 1H), 7.77 (d, 1H), 7.74 (br d, 1H), 7.62-7.55 (m, 2H), 6.53 (s, 4H), 4.05 (s, 2H), 2.78 (t, 2H), 2.59 (t, 2H), 2.34 (s, 6H), 1.78 (p, 2H)

30

II-060 (E)- 3-(2,5-Dimethoxy-phenyl)-1-{4-[(3-dimethylamino-propylamino)-methyl]-phenyl}-propenone

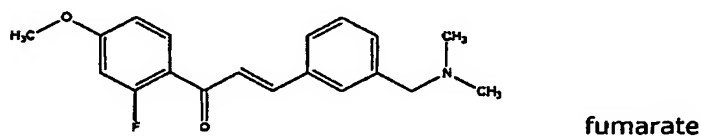


General procedure F gave the title compound as yellow crystals in 9% yield

5

$^1\text{H-NMR}$ (300 MHz, DMSO-d_6) δ 8.15 (d, 2H), 8.04 (d, 1H), 7.90 (d, 1H), 7.64 (d, 2H), 7.56 (t, 1H), 7.04 (d, 2H), 6.53 (s, 4H), 4.07 (s, 2H), 3.84 (s, 3H), 3.80 (s, 3H), 2.81 (t, 2H), 2.74 (t, 2H), 2.45 (s, 6H), 1.86 (p, 2H)

- 10 **II-061** (*E*)- 3-(3-Dimethylaminomethyl-phenyl)-1-(2-fluoro-4-methoxy-phenyl)-propenone

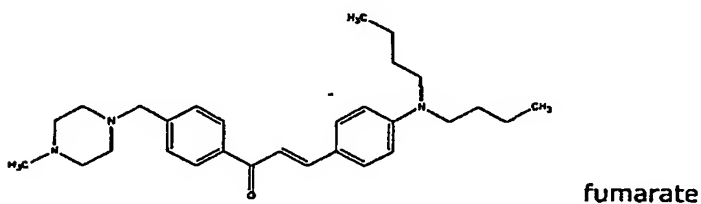


- 15 General procedure F gave the title compound as slightly yellow crystals in 60% yield

$^1\text{H-NMR}$ (300 MHz, DMSO-d_6) δ 7.84 (t, 1H), 7.69 (br, 2H), 7.65 (d, 1H), 7.49 (dd, 1H), 7.43 – 7.40 (m, 2H), 6.97 (dd, 1H), 6.96 (t, 1H), 6.60 (s, 2H), 3.88 (s, 3H), 3.52 (s, 2H), 2.21 (s, 6H)

20

- II-062** (*E*)- 3-(4-Dibutylamino-phenyl)-1-[4-(4-methyl-piperazin-1-ylmethyl)-phenyl]-propenone

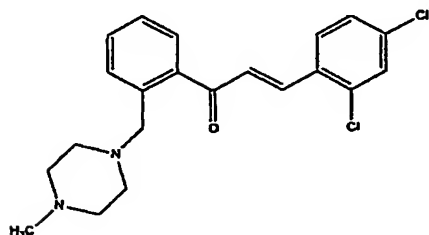


25

General procedure F gave the title compound as orange crystals in 2% yield

- $^1\text{H-NMR}$ (300 MHz, DMSO-d_6) δ 8.05 (d, 2H), 7.67-7.54 (m, 4H), 7.46 (d, 2H), 6.68 (d, 2H), 6.59 (s, 4H), 3.59 (s, 2H), 3.34 (t, 4H), 2.71 (br, 4H), 2.41 (s, 3H), 1.52-1.47 (m, 4H), 1.39-1.27 (m, 4H), 0.92 (t, 6H)

30

II-063. (*E*)- 3-(2,4-Dichloro-phenyl)-1-[2-(4-methyl-piperazin-1-ylmethyl)-phenyl]-propenone

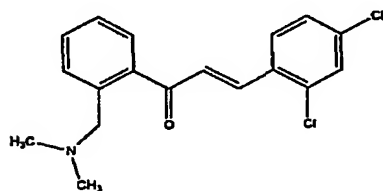
fumarate

5

General procedure F gave the title compound as white crystals in 50% yield

¹H-NMR(300 MHz, DMSO-d₆) δ 8.06 (d, 1H), 7.71- 7.70 (m, 1H), 7.52- 7.39 (m, 6H), 7.30 (d, 1H), 6.56 (s, 4H), 3.61 (s, 2H), 2.49 (br, under DMSO, 4H), 2.35 (br, 4H), 2.27 (s, 3H)

10

II-064 (*E*)- 3-(2,4-Dichloro-phenyl)-1-(2-dimethylaminomethyl-phenyl)-propenone

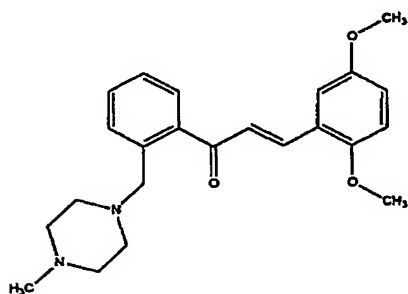
fumarate

15

General procedure F gave the title compound as white crystals in 31% yield

¹H-NMR(300 MHz, DMSO-d₆) δ 8.10 (d, 1H), 7.71 (d, 1H), 7.62- 7.59 (m, 2H), 7.55 - 7.39 (m, 6H), 6.59 (s, 2H), 3.73 (s, 2H), 2.19 (s, 6H)

20

II-065 (*E*)- 3-(2,5-Dimethoxy-phenyl)-1-[2-(4-methyl-piperazin-1-ylmethyl)-phenyl]-propenone

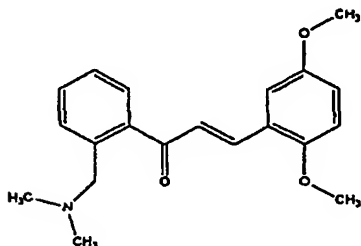
25

General procedure F gave the title compound as brown oil in 69% yield

$^1\text{H-NMR}$ (300 MHz, CDCl_3) δ 7.51 (d, 2H), 7.41-7.27 (m, 3H), 7.08-7.03 (m, 2H), 6.93 – 6.82 (m, 2H), 3.79 (s, 3H), 3.78 (s, 3H), 3.75 (s, 2H), 2.38-2.19 (br, 8H), 2.19 (s, 3H)

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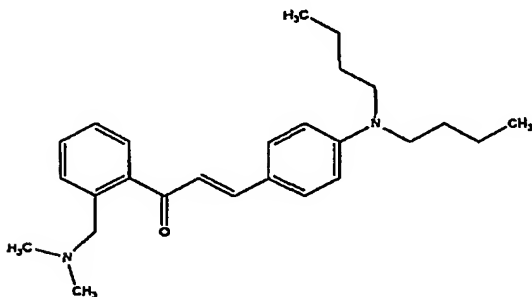
II-066 (*E*)- 3-(2,5-Dimethoxy-phenyl)-1-(2-dimethylaminomethyl-phenyl)-propenone



General procedure F gave the title compound as brown oil in 82% yield

10 $^1\text{H-NMR}$ (300 MHz, CDCl_3) δ 7.58 (d, 1H), 7.43-7.32 (m, 4H), 7.13-7.07 (m, 2H), 6.95 – 6.83 (m, 2H), 3.81 (s, 3H), 3.80 (s, 3H), 3.56 (s, 2H), 2.19 (s, 6H)

II-067 (*E*)- 3-(4-Dibutylamino-phenyl)-1-(2-dimethylaminomethyl-phenyl)-propenone



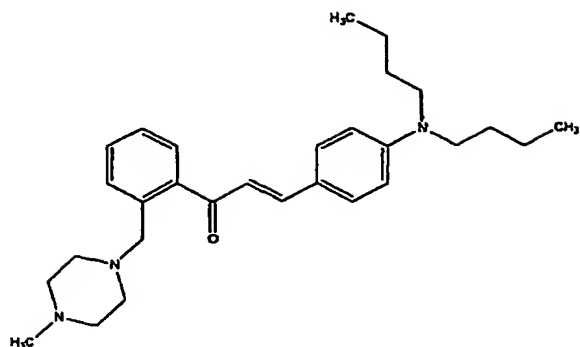
15

General procedure F gave the title compound as brown oil in 49% yield

20 $^1\text{H-NMR}$ (300 MHz, CDCl_3) δ 7.46 (d, 1H), 7.42-7.28 (m, 5H), 7.21 (d, 1H), 6.85 (d, 1H), 6.59 (d, 2H), 3.53 (s, 2H), 3.30 (t, 4H), 2.16 (s, 6H), 1.61-1.53 (m, 4H), 1.40-1.35 (m, 4H), 0.96 (t, 6H)

II-068 (*E*)- 3-(4-Dibutylamino-phenyl)-1-[2-(4-methyl-piperazin-1-ylmethyl)-phenyl]-propenone

25

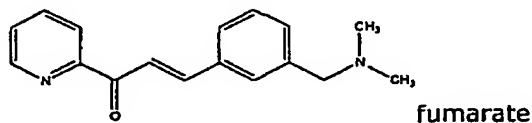


General procedure F gave the title compound as orange oil in 71% yield

5

$^1\text{H-NMR}$ (300 MHz, CDCl_3) δ 7.38-7.28 (m, 6H), 7.18 (d, 1H), 6.82 (d, 1H), 6.59 (d, 2H), 3.60 (s, 2H), 3.30 (t, 4H), 2.39-2.26 (br, 8H), 2.19 (s, 3H), 1.63-1.53 (m, 4H), 1.40-1.30 (m, 4H)

10 **II-069**• (E)- 3-(3-Dimethylaminomethyl-phenyl)-1-pyridin-2-yl-propenone

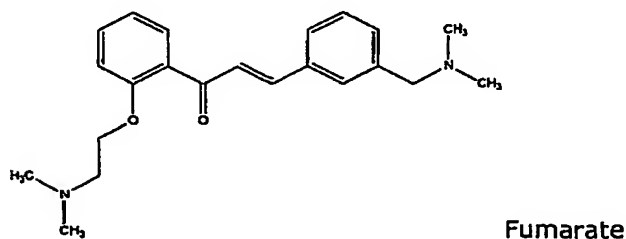


General procedure I gave the title compound as white crystals in 30% yield

15

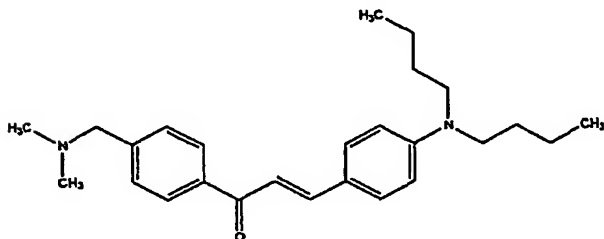
$^1\text{H-NMR}$ (300 MHz, DMSO-d_6) δ 8.82 (d, 1H), 8.28 (d, 1H), 8.14-8.03 (m, 2H), 7.87 (d, 1H), 7.79-7.69 (m, 2H), 7.56-7.43 (m, 2H), 7.11-7.04 (m, 1H), 6.60 (s, 2H), 3.58 (s, 2H), 2.25 (s, 6H)

20 **II-070** (E)- 1-[2-(2-Dimethylamino-ethoxy)-phenyl]-3-(3-dimethylaminomethyl-phenyl)-propenone



25 General procedure F gave the title compound as yellow crystals in 32% yield

$^1\text{H-NMR}$ (300 MHz, CDCl_3) δ 7.73-7.70 (m, 2H), 7.62-7.43 (m, 6H), 7.23 (d, 1H), 7.09 (t, 1H), 6.60 (s, 4H), 4.27 (t, 2H), 3.63 (s, 2H), 2.83 (t, 2H), 2.29 (s, 12H)

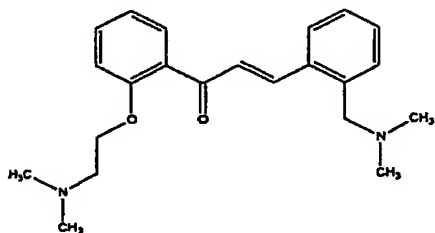
II-071 (E)- 3-(4-Dibutylamino-phenyl)-1-(4-dimethylaminomethyl-phenyl)-propenone

5

General procedure F gave the title compound as orange oil in 28% yield

¹H-NMR(300 MHz, CDCl₃) δ 7.98 (d, 2H), 7.79 (d, 1H), 7.53 (d, 2H), 7.44 (d, 2H), 7.33 (d, 1H), 6.64 (d, 2H), 6.63 (s, 2H), 4.14 (q, 4H), 2.28 (s, 6H), 1.66-1.57 (m, 4H), 1.45-1.38 (m, 4H), 0.99 (t, 6H)

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II-072 (E)- 1-[2-(2-Dimethylamino-ethoxy)-phenyl]-3-(2-dimethylaminomethyl-phenyl)-propenone

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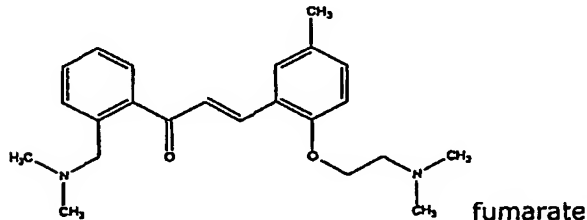
General procedure F gave the title compound as brown oil in 20% yield

¹H-NMR(300 MHz, CDCl₃) δ 8.10 (d, 1H), 7.77-7.74 (m, 1H), 7.63 (dd, 1H), 7.47-7.27 (m, 5H), 7.06-6.97 (m, 2H), 4.15 (t, 2H), 3.47 (s, 2H), 2.71 (t, 2H), 2.25 (s, 6H), 2.19 (s, 6H)

20

II-073 (E)- 3-[2-(2-Dimethylamino-ethoxy)-5-methyl-phenyl]-1-(2-dimethylaminomethyl-phenyl)-propenone

25

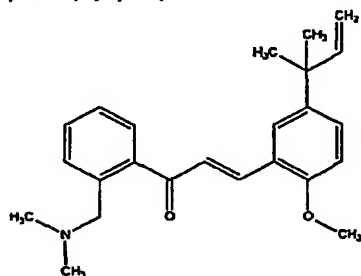


General procedure F gave the title compound as yellow needles in 25% yield

$^1\text{H-NMR}$ (300 MHz, DMSO) δ 11 (br, 2H), 7.65 (d, 1H), 7.64 (d, 1H), 7.56 (d, 1H), 7.53-7.46 (m, 3H), 7.30 (d, 1H), 7.22 (dd, 1H), 6.99 (d, 1H), 6.58 (s, 4H), 4.20 (t, 2H), 3.72 (s, 2H), 2.95 (t, 2H), 2.38 (s, 6H), 2.27 (s, 3H), 2.23 (s, 6H)

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II-074 (*E*)- 3-[5-(1,1-Dimethyl-allyl)-2-methoxy-phenyl]-1-(2-dimethylaminomethyl-phenyl)-propenone

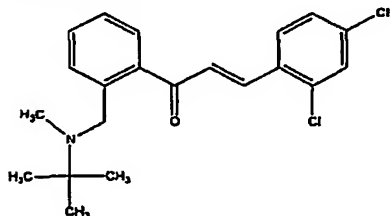


General procedure F gave the title compound as yellow oil in 26% yield

10

$^1\text{H-NMR}$ (300 MHz, CDCl_3) δ 7.58 (d, 1H), 7.53 (d, 1H), 7.44-7.33 (m, 5H), 7.15 (d, 1H), 6.86 (d, 1H), 6.01 (dd, 1H), 5.10-5.04 (m, 2H), 3.83 (s, 3H), 3.57 (s, 2H), 2.16 (s, 6H), 1.41 (s, 6H)

II-075 (*E*)- 1-{2-[(*tert*-Butyl-methyl-amino)-methyl]-phenyl}-3-(2,4-dichloro-phenyl)-propenone

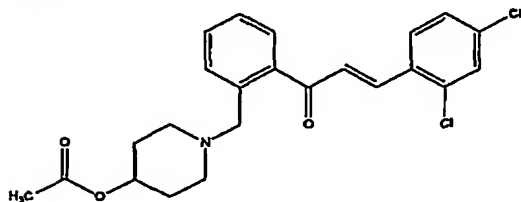


General procedure F gave the title compound as orange oil in 33% yield

20

$^1\text{H-NMR}$ (300 MHz, CDCl_3) δ 7.48-7.12 (m, 8H), 6.82 (d, 1H), 3.57 (s, 2H), 1.81 (s, 3H), 0.90 (s, 9H)

II-076 (*E*)- Acetic acid 1-{2-[3-(2,4-dichloro-phenyl)-acryloyl]-benzyl}-piperidin-4-yl ester

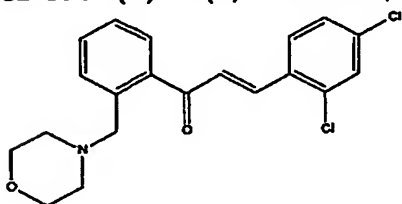


General procedure F gave the title compound as orange oil in 45% yield

¹H-NMR(300 MHz, CDCl₃) δ 7.60 (d, 1H), 7.48 (d, 1H), 7.45-7.29 (m, 6H), 6.97 (d, 1H), 4.74-4.68 (m, 1H), 3.61 (s, 2H), 2.61-2.54 (m, 2H), 2.25-2.17 (m, 2H), 2.02 (s, 3H), 1.77-1.71 (m, 2H), 1.62-1.49 (m, 2H)

5

II-077 (E)- 3-(2,4-Dichloro-phenyl)-1-(2-morpholin-4-ylmethyl-phenyl)-propenone



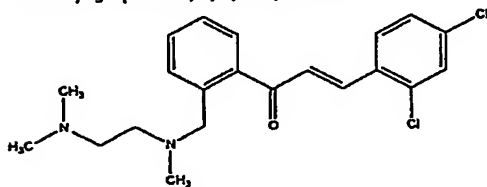
General procedure F gave the title compound as yellow oil in 38% yield

10

¹H-NMR(300 MHz, CDCl₃) δ 7.62 (d, 1H), 7.565 (d, 1H), 7.54-7.30 (m, 6H), 6.99 (d, 1H), 3.62 (s, 2H), 3.55 (t, 4H), 2.37 (t, 4H)

15

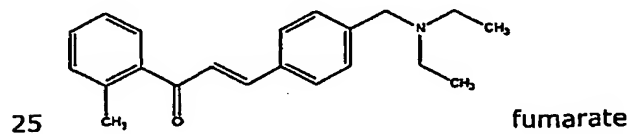
II-078 (E)- 3-(2,4-Dichloro-phenyl)-1-(2-[(2-dimethylamino-ethyl)-methyl-amino]-methyl)-phenyl)-propenone



General procedure F gave the title compound as orange oil in 10% yield

20 ¹H-NMR(300 MHz, CDCl₃) δ 7.63 (d, 1H), 7.58 (d, 1H), 7.45-7.29 (m, 6H), 6.99 (d, 1H), 3.67 (s, 2H), 2.49-2.44 (m, 2H), 2.35-2.30 (m, 2H), 2.16 (s, 6H), 2.11 (s, 3H)

II-079 (E)-3-(4-Diethylaminomethyl-phenyl)-1-o-tolyl-propenone

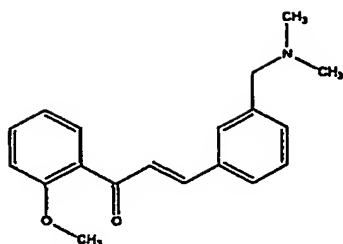


25

General procedure F gave the title compound as slightly yellow crystals in 32% yield

30 ¹H-NMR(300 MHz, DMSO) δ 7.77 (d, 2H), 7.62 (dd, 1H), 7.49-7.32 (m, 7H), 6.60 (s, 3H), 3.79 (s, 2H), 2.64 (q, 4H), 2.38 (s, 3H), 1.05 (t, 6H)

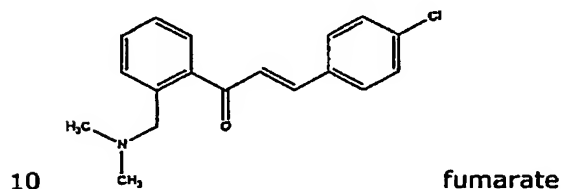
II-080 (E)- 3-(3-Dimethylaminomethyl-phenyl)-1-(2-methoxy-phenyl)-propenone



General procedure F gave the title compound as orange oil in 22% yield

5 $^1\text{H-NMR}$ (300 MHz, CDCl_3) δ 7.52 (d, 1H), 7.51 (dd, 1H), 7.44-7.37 (m, 3H), 7.28-7.26 (m, 2H), 7.27 (d, 1H), 6.99-6.91 (m, 2H), 3.82 (s, 3H), 3.37 (s, 2H), 2.18 (s, 6H)

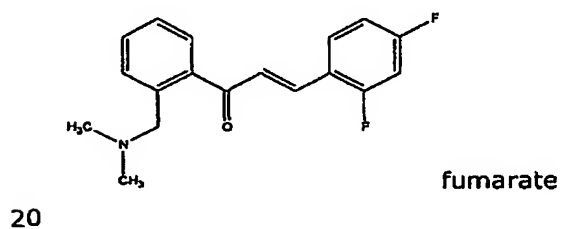
II-081 (E)- 3-(4-Chloro-phenyl)-1-(2-dimethylaminomethyl-phenyl)-propenone



General procedure F gave the title compound as white crystals in 22% yield

15 $^1\text{H-NMR}$ (300 MHz, DMSO) δ 7.80 (d, 2H), 7.59 (d, 1H), 7.55-7.41 (m, 5H), 7.37 (s, 2H), 6.60 (s, 2H), 3.71 (s, 2H), 2.19 (s, 6H)

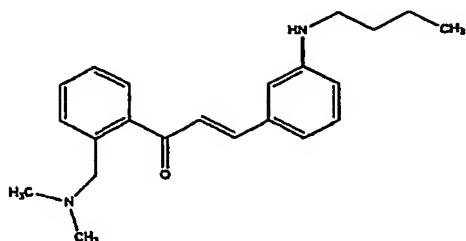
II-082 (E)- 3-(2,4-Difluoro-phenyl)-1-(2-dimethylaminomethyl-phenyl)-propenone



General procedure F gave the title compound as white crystals in 46% yield

25 $^1\text{H-NMR}$ (300 MHz, DMSO) δ 8.09-8.02 (m, 1H), 7.55-7.19 (m, 7H), 7.17-7.16 (m, 1H), 6.60 (s, 2H), 3.66 (s, 2H), 2.15 (s, 6H)

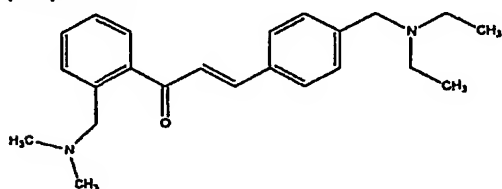
II-083 (E)- 3-(3-Butylamino-phenyl)-1-(2-dimethylaminomethyl-phenyl)-propenone



General procedure F gave the title compound as brown oil in 34% yield

- 5 $^1\text{H-NMR}$ (300 MHz, CDCl_3) δ 7.45-7.32 (m, 4H), 7.21-7.16 (m, 1H), 7.17 (d, 1H), 7.01 (d, 1H), 6.87 (d, 1H), 6.74 (t, 1H), 6.64 (dd, 1H), 3.69 (br, 1H), 3.60 (s, 2H), 3.14 (t, 2H), 2.15 (s, 6H), 1.68-1.61 (m, 2H), 1.49-1.39 (m, 2H), 0.98 (t, 3H)

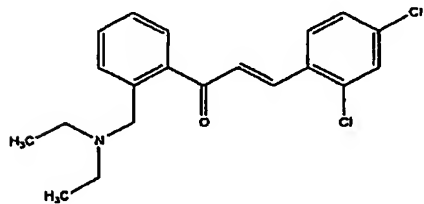
- II-084.** (E)- 3-(4-Diethylaminomethyl-phenyl)-1-(2-dimethylaminomethyl-phenyl)-propenone



General procedure F gave the title compound as brown oil in 20% yield

- 15 $^1\text{H-NMR}$ (300 MHz, CDCl_3) δ 7.46 (d, 2H), 7.41-7.20 (m, 7H), 7.03 (d, 1H), 3.57 (s, 2H), 3.53 (s, 2H), 2.52 (q, 4H), 2.13 (s, 6H), 1.04 (t, 6H)

- II-085** (E)- 3-(2,4-Dichloro-phenyl)-1-(2-diethylaminomethyl-phenyl)-propenone



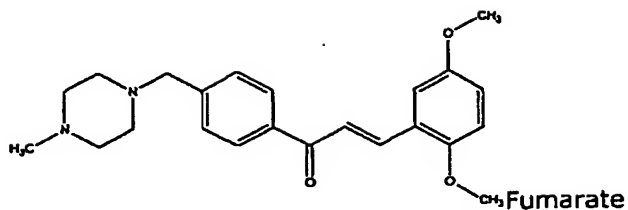
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Fumarate

General procedure F gave the title compound as white powder in 28% yield

- 25 $^1\text{H-NMR}$ (300 MHz, DMSO) δ 13.07 (br, 1H), 8.08 (d, 1H), 7.72 (d, 1H), 7.54-7.37 (m, 6H), 7.32 (d, 1H), 6.61 (s, 2H), 3.72 (s, 2H), 2.40 (q, 4H), 0.85 (t, 6H)

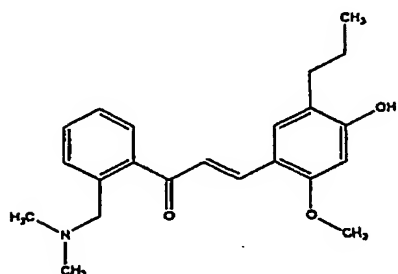
- II-086** (E)- 3-(2,5-Dimethoxy-phenyl)-1-[4-(4-methyl-piperazin-1-ylmethyl)-phenyl]-propenone



General procedure F gave the title compound as yellow crystals in 5% yield

¹H-NMR (300 MHz, DMSO) δ 8.11 (d, 2H), 8.03 (d, 1H), 7.96 (d, 1H), 7.55-7.54 (m, 1H), 7.50 (d, 2H), 7.06-7.05 (m, 2H), 6.59 (s, 4H), 3.85 (s, 3H), 3.80 (s, 3H), 3.60 (s, 2H), 2.65 (br, 4H), 2.56-2.49 (under DMSO, 2H), 2.37 (s, 3H)

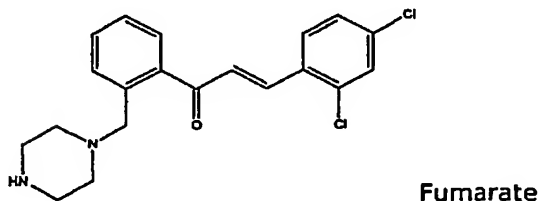
II-087 (E)- 1-(2-Dimethylaminomethyl-phenyl)-3-(4-hydroxy-2-methoxy-5-propyl-phenyl)-propenone



General procedure F, using acidic work-up, gave the title compound as red oil in 20% yield

¹H-NMR (300 MHz, DMSO) δ 10.23 (br, 1H), 7.65 (d, 1H), 7.60-7.47 (m, 5H), 7.17 (d, 1H), 6.62 (s, 1H), 3.88 (s, 3H), 3.61 (s, 2H), 2.59 (t, 2H), 2.18 (s, 6H), 1.73-1.63 (m, 2H), 1.01 (t, 3H)

II-088 (E)- 3-(2,4-Dichloro-phenyl)-1-(2-piperazin-1-ylmethyl-phenyl)-propenone

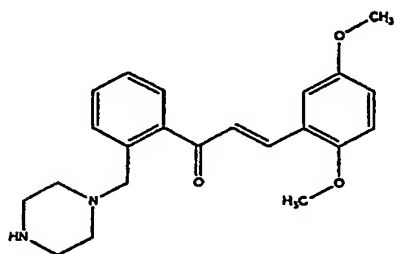


General procedure F gave the title compound as white powder in 27% yield

¹H-NMR (300 MHz, DMSO) δ 8.08 (d, 1H), 7.72 (d, 1H), 7.53-7.40 (m, 6H), 7.40 (d, 1H), 6.45 (s, 2H), 3.64 (s, 2H), 2.8 (br, 4H), 2.4 (br, 4H)

II-089. (*E*)-3-(2,5-Dimethoxy-phenyl)-1-(2-piperazin-1-ylmethyl-phenyl)-propenone

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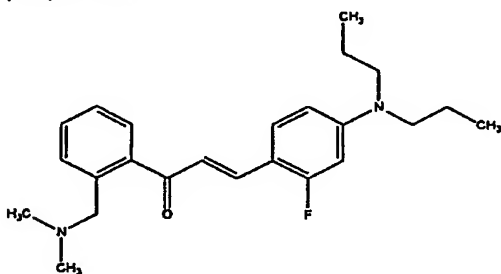
Fumarate

General procedure F gave the title compound as white powder in 30% yield

10 ¹H-NMR (300 MHz, DMSO) δ 10.37 (br, 2H), 7.53 (d, 1H), 7.44-7.33 (m, 5H), 7.25 (d, 1H), 7.00 (d, 2H), 6.44 (s, 2H), 3.75 (s, 3H), 3.75 (s, 3H), 3.59 (s, 2H), 2.78 (br, 4H), 2.37 (br, 4H)

II-090 (*E*)-1-(2-Dimethylaminomethyl-phenyl)-3-(4-dipropylamino-2-fluoro-phenyl)-propenone

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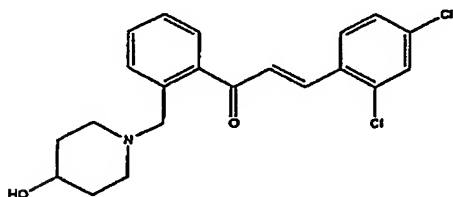


General procedure F gave the title compound as brown oil in 39% yield

20 ¹H-NMR(300 MHz, CDCl₃) δ 7.54-7.27 (m, 6H), 6.85 (d, 1H), 6.32 (dd, 1H), 6.18 (dd, 1H), 3.47 (s, 2H), 3.18 (t, 4H), 2.08 (s, 6H), 1.61-1.49 (m, 4 H), 0.87 (t, 6H)

II-091 (*E*)-3-(2,4-Dichloro-phenyl)-1-[2-(4-hydroxy-piperidin-1-ylmethyl)-phenyl]-propenone

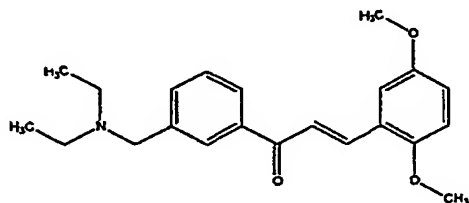
25



General procedure F gave the title compound as brown semi-solid in 39% yield

¹H-NMR (300 MHz, DMSO) δ 8.05 (d, 1H), 7.70 (d, 1H), 7.50-7.25 (m, 7H), 4.46 (br, 1H), 3.55 (s, 2H), 3.35-3.32 (m, 2H), 2.47-2.44 (m, 2H (under DMSO)), 2.00-1.93 (m, 2H), 1.53-1.49 (m, 2H), 1.24-1.21 (m, 2H)

II-092 (*E*)-1-(3-Diethylaminomethyl-phenyl)-3-(2,5-dimethoxy-phenyl)-propenone

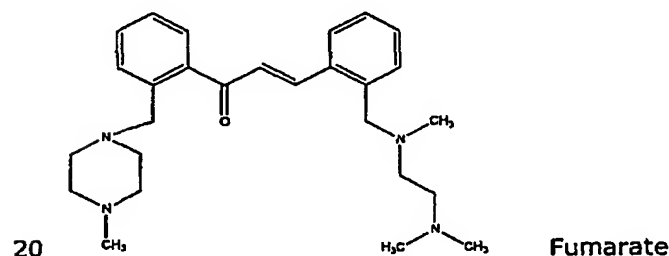


10

General procedure F gave the title compound as yellow oil in 41% yield

¹H-NMR (300 MHz, DMSO) δ 8.07 (d, 1H), 7.95 (s, 1H), 7.87 (d, 1H), 7.59 (d, 1H), 7.58 (d, 1H), 7.44 (t, 1H), 7.18 (d, 1H), 6.94 (dd, 1H), 6.88 (d, 1H), 3.87 (s, 3H), 2.82 (s, 3H), 1.53-1.49 (m, 2H), 1.24-1.21 (m, 2H)

II-093 (*E*)-3-(2-([(2-Dimethylamino-ethyl)-methyl-amino]-methyl)-phenyl)-1-[2-(4-methyl-piperazin-1-ylmethyl)-phenyl]-propenone



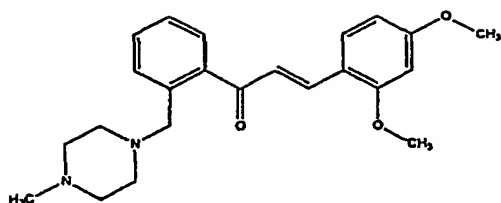
20

General procedure F gave the title compound as white crystals in 39% yield

¹H-NMR (300 MHz, DMSO) δ 7.71-7.68 (m, 1H), 7.50 (d, 1H), 7.27-7.11 (m, 7H), 6.86 (d, 1H), 6.34 (s, 4H), 3.38 (s, 2H), 3.27 (s, 2H), 2.40 (t, 2H), 2.24 (t, 2H), 2.15 (s, 6H), 2.11 (br, 4H), 1.94 (s, 3H), 1.79 (s, 3H)

II-094 (*E*)-3-(2,4-Dimethoxy-phenyl)-1-[2-(4-methyl-piperazin-1-ylmethyl)-phenyl]-propenone

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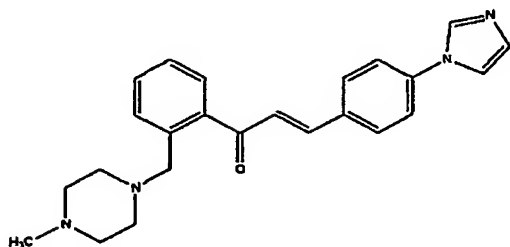


Fumarate

General procedure F gave the title compound as white crystals in 48% yield

- 5 $^1\text{H-NMR}$ (300 MHz, DMSO) δ 7.46 (d, 1H), 7.25 (d, 1H), 7.19-7.12 (m, 5H), 6.82 (d, 1H), 6.38-6.33 (m, 2H), 6.36 (s, 4H), 3.58 (s, 3H), 3.58 (s, 3H), 3.30 (s, 2H), 2.25 (br, 4H), 1.94 (s, 3H)

II-095 (*E*)-3-(4-Imidazol-1-yl-phenyl)-1-[2-(4-methyl-piperazin-1-ylmethyl)-phenyl]-propenone
10 propenone

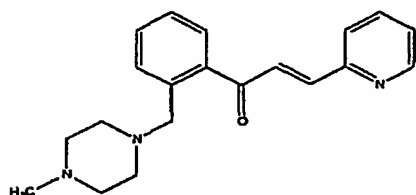


Fumarate

General procedure F gave the title compound as white crystals in 46% yield

- 15 $^1\text{H-NMR}$ (300 MHz, DMSO) δ 8.38 (t, 1H), 7.91 (d, 2H), 7.85 (t, 1H), 7.74 (d, 2H), 7.44-7.31 (m, 6H), 7.14 (t, 1H), 6.60 (s, 4H), 3.60 (s, 2H), 2.34 (br, 8H), 2.19 (s, 3H)

II-096 (*E*)-1-[2-(4-Methyl-piperazin-1-ylmethyl)-phenyl]-3-pyridin-2-yl-propenone
20

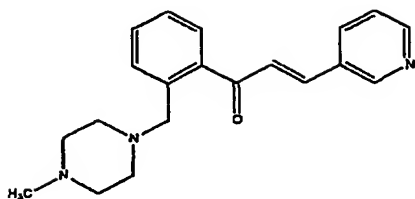


Fumarate

General procedure F gave the title compound as white crystals in 58% yield

- 25 $^1\text{H-NMR}$ (300 MHz, DMSO) δ 8.64 (d, 1H), 8.85 (td, 1H), 7.76 (d, 1H), 7.48-7.37 (m, 6H), 7.19 (d, 1H), 6.68 (s, 2H), 3.55 (s, 2H), 2.29 (br, 8H), 2.13 (s, 3H)

II-097 (*E*)-1-[2-(4-Methyl-piperazin-1-ylmethyl)-phenyl]-3-pyridin-3-yl-propenone



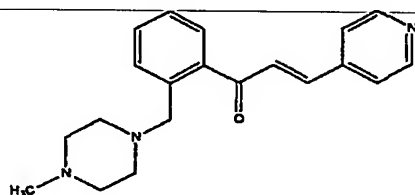
Fumarate

General procedure F gave the title compound as white crystals in 19% yield

- 5 ¹H-NMR (300 MHz, DMSO) δ 8.88 (d, 1H), 8.58 (dd, 1H), 8.21 (d, 1H), 7.48-7.39 (m, 5H), 7.37 (d, 1H), 7.29 (d, 1H), 6.59 (s, 4H), 3.60 (s, 2H), 2.41 (br, 4H), 2.33 (br, 4H), 2.21 (s, 3H)

II-098 (E)- 1-[2-(4-Methyl-piperazin-1-ylmethyl)-phenyl]-3-pyridin-4-yl-propenone

10



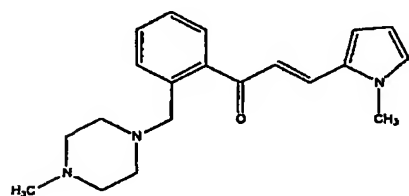
Fumarate

General procedure F gave the title compound as off-white crystals in 6% yield

- 15 ¹H-NMR (300 MHz, DMSO) δ 8.61 (d, 2H), 7.70 (d, 2H), 7.47-7.40 (m, 5H), 7.20 (d, 1H), 6.60 (s, 4H), 3.60 (s, 2H), 2.40-2.32 (br 8H), 2.21 (s, 3H)

II-099 (E)- 1-[2-(4-Methyl-piperazin-1-ylmethyl)-phenyl]-3-(1-methyl-1H-pyrrol-2-yl)-propenone

20



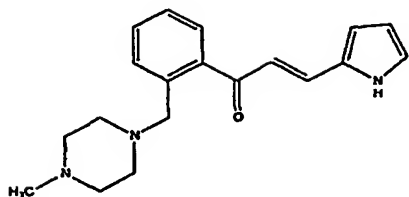
Fumarate

General procedure F gave the title compound as yellow crystals in 44% yield

- 25 ¹H-NMR (300 MHz, DMSO) δ 7.44-7.36 (m, 4H), 7.27 (d, 1H), 7.05 (t, 1H), 6.87 (d, 1H), 6.86 (dd, 1H), 6.60 (s, 4H), 6.14 (dd, 1H), 3.65 (s, 3H), 3.57 (s, 2H), 2.42-3.30 (br, 8H), 2.20 (s, 3H)

II-100 (E)- 1-[2-(4-Methyl-piperazin-1-ylmethyl)-phenyl]-3-(1H-pyrrol-2-yl)-propenone

30



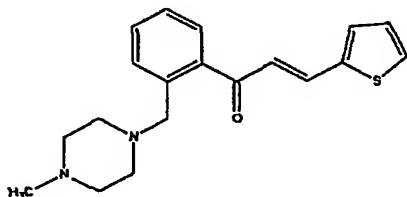
Fumarate

General procedure F gave the title compound as orange crystals in 24% yield

- 5 $^1\text{H-NMR}$ (300 MHz, DMSO) δ 11.58 (1H), 7.44-7.35 (m, 4H), 7.10 (d, 1H), 7.08-7.06 (m, 1H), 6.83 (d, 1H), 6.61-6.60 (m, 1H), 6.59 (s, 4H), 6.19-6.17 (m, 1H), 3.55 (s, 2H), 2.47 (br, 4H), 2.35 (br, 4H), 2.24 (s, 3H)

II-101 (E)- 1-[2-(4-Methyl-piperazin-1-ylmethyl)-phenyl]-3-thiophen-2-yl-propenone

10

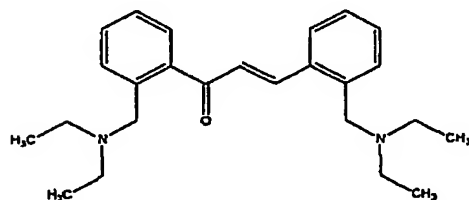


Oxalate

General procedure F gave the title compound as slightly yellow crystals in 96% yield

- 15 $^1\text{H-NMR}$ (300 MHz, DMSO) δ 7.76 (d, 1H), 7.58 (d, 1H), 7.53-7.41 (m, 6H), 7.16 (dd, 1H), 6.93 (d, 1H), 3.65 (s, 2H), 3.05 (br, 4H), 2.66 (s, 3H), 2.55 (br, 4H)

II-102 (E)- 1,3-Bis-(2-diethylaminomethyl-phenyl)-propenone



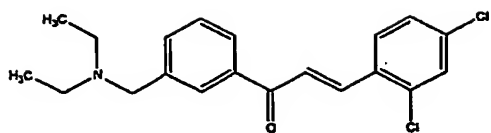
Fumarate

20

General procedure F gave the title compound as white powder in 15% yield

- 25 $^1\text{H-NMR}$ (300 MHz, DMSO) δ 13.04 (br, 2H), 7.90-7.85 (m, 1H), 7.84 (d, 1H), 7.46-7.28 (m, 7H), 7.03 (d, 1H), 6.62 (s, 4H), 3.69 (s, 2H), 3.47 (s, 2H), 2.43 (q, 4H), 2.29 (q, 4H), 0.87 (t, 6H), 0.76 (t, 6H)

II-103 (E)- 3-(2,4-Dichloro-phenyl)-1-(3-diethylaminomethyl-phenyl)-propenone

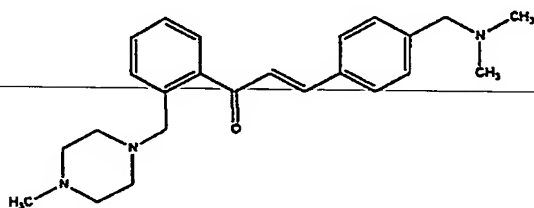


General procedure F gave the title compound as orange oil in 15% yield

- 5 $^1\text{H-NMR}$ (300 MHz, CDCl_3) δ 8.09 (d, 1H), 7.96 (s, 1H), 7.87 (d, 1H), 7.69 (d, 1H), 7.61 (d, 1H), 7.50-7.32 (m, 3H), 7.30 (dd, 1H), 3.65 (s, 2H), 2.55 (q, 4H), 1.05 (t, 6H)

II-104. (E)- 3-(4-Dimethylaminomethyl-phenyl)-1-[2-(4-methyl-piperazin-1-ylmethyl)-phenyl]-propenone

10



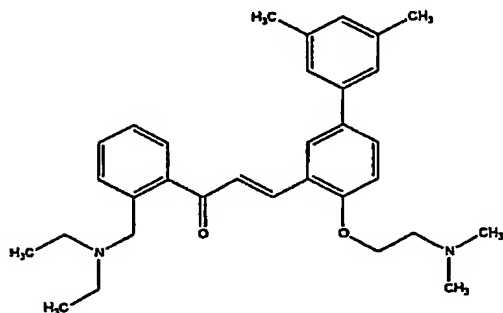
Fumarate

General procedure F gave the title compound as white crystals in 23% yield

- 15 $^1\text{H-NMR}$ (300 MHz, DMSO) δ 7.72 (d, 2H), 7.43-7.38 (m, 6H), 7.27 (d, 1H), 7.24 (d, 1H), 6.57 (s, 6H), 3.70 (s, 2H), 3.59 (s, 2H), 2.36 (br, 4H), 2.32 (s, 6H), 2.26 (s, 3H)

II-105 (E)- 1-(2-Diethylaminomethyl-phenyl)-3-[4-(2-dimethylamino-ethoxy)-3',5'-dimethyl-biphenyl-3-yl]-propenone

20

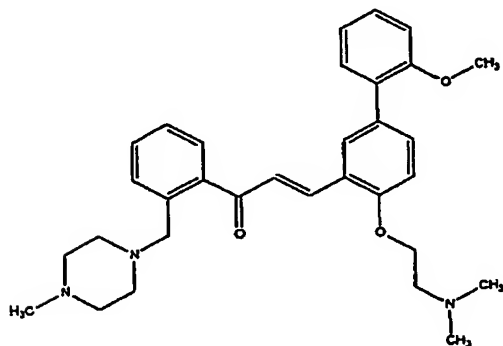


Fumarate

General procedure F gave the title compound as green flakes in 33% yield

- 25 $^1\text{H-NMR}$ (DMSO) δ 8.02 (d, 1H), 7.67 (dd, 1H), 7.61 (d, 1H), 7.47-7.38 (m 4H), 7.37 (d, 1H), 7.31 (br, 2H), 7.15 (d, 1H), 6.96 (br, 1H), 6.59 (s, 3H), 4.19 (t, 2H), 3.68 (s, 2H), 2.78 (t, 2H), 2.40 (q, 4H), 2.39 (s, 6H), 2.24 (s, 6H), 0.86 (t, 6H)

II-106 (*E*)- 3-[4-(2-Dimethylamino-ethoxy)-2'-methoxy-biphenyl-3-yl]-1-[2-(4-methyl-piperazin-1-ylmethyl)-phenyl]-propenone



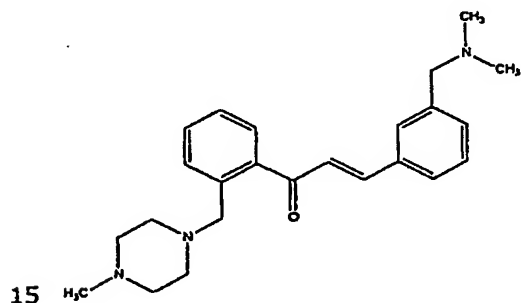
Fumarate

5

General procedure F gave the title compound as yellow crystals in 40% yield

¹H-NMR(300 MHz, DMSO-d₆) δ 7.85 (d, 1H), 7.59 (d, 1H), 7.56-7.33 (m, 7H), 7.25 (d, 1H), 7.16-7.12 (dd, 2H), 7.04 (t, 1H), 6.61 (s, 6H), 4.22 (t, 2H), 3.79 (s, 3H), 3.60 (s, 10 2H), 2.81 (t, 2H), 2.50-2.30 (broad, 8H), 2.28 (s, 6H), 2.22 (s, 3H)

II-107 (*E*)- 3-(3-Dimethylaminomethyl-phenyl)-1-[2-(4-methyl-piperazin-1-ylmethyl)-phenyl]-propenone



Fumarate

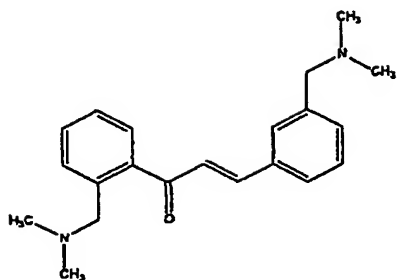
15

General procedure F gave the title compound as off-white crystals in 33% yield

¹H-NMR (DMSO) δ 7.70-7.67 (m, 2H), 7.50-7.40 (m, 6H), 7.25 (d, 1H), 7.21 (d, 1H), 6.56 20 (s, 4H), 3.67 (s, 2H), 3.57 (s, 2H), 2.34 (br, 4H), 2.32 (br, 4H), 2.30 (s, 6H), 2.20 (s, 3H)

II-108 (*E*)- 3-(3-Dimethylaminomethyl-phenyl)-1-(2-dimethylaminomethyl-phenyl)-propenone

25



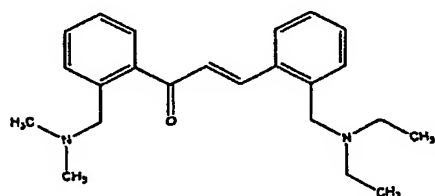
Fumarate

General procedure F gave the title compound as white crystals in 32% yield

- 5 $^1\text{H-NMR}$ (DMSO) δ 7.78 (s, 1H), 7.72 (br, 1H), 7.73-7.34 (m, 8H), 6.57 (s, 4H), 3.82 (s, 2H), 3.72 (s, 2H), 2.40 (s, 6H), 2.21 (s, 6H)

II-109 (E)- 3-(2-Diethylaminomethyl-phenyl)-1-(2-dimethylaminomethyl-phenyl)-propenone

10



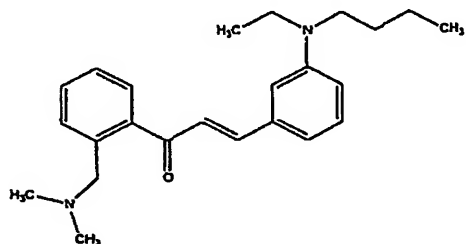
Fumarate

General procedure F gave the title compound as white crystals in 54% yield

- 15 $^1\text{H-NMR}$ (DMSO) δ 7.91-7.87 (m, 1H), 7.87 (d, 1H), 7.53-7.32 (m, 7H), 7.09 (d, 1H), 6.61 (s, 4H), 3.67 (s, 2H), 3.50 (s, 2H), 2.31 (q, 4H), 2.19 (s, 6H), 0.78 (t, 6H)

II-110 (E)- 3-[3-(Butyl-ethyl-amino)-phenyl]-1-(2-dimethylaminomethyl-phenyl)-propenone

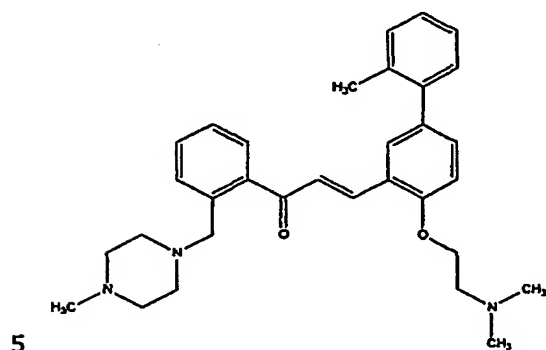
20



General procedure F gave the title compound as yellow oil in 3% yield

- 25 $^1\text{H-NMR}$ (DMSO) δ 7.61-7.29 (m, 4H), 7.23-7.15 (m, 2H), 6.99 (d, 1H), 6.91-6.76 (m, 2H), 6.68 (dd, 1H), 3.53 (s, 2H), 3.37 (q, 2H), 3.37 (q, 2H), 2.14 (s, 6H), 1.60-1.52 (m, 2H), 1.43-1.26 (m, 2H), 1.15 (t, 3H), 0.96 (t, 3H)

II-111 (*E*)- 3-[4-(2-Dimethylamino-ethoxy)-2'-methyl-biphenyl-3-yl]-1-[2-(4-methyl-piperazin-1-ylmethyl)-phenyl]-propenone

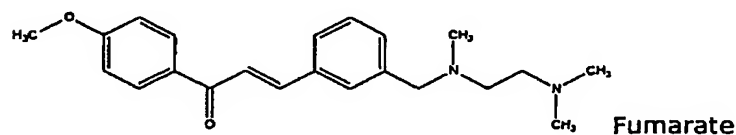


General procedure F gave the title compound as pale brown crystals in 39% yield

¹H-NMR(300 MHz, CDCl₃) δ 7.62 (d, 1H), 7.55 (d, 1H), 7.41-7.24 (m, 9H), 7.10 (d, 1H), 6.96 (d, 1H), 4.15 (t, 2H), 3.61 (s, 2H), 2.73 (t, 2H), 2.38 (br, 4H), 2.30 (br, 4H), 2.30 (s, 3H), 2.26 (s, 6H), 2.18 (s, 3H)

II-112 (*E*)- 3-(3-[(2-Dimethylamino-ethyl)-methyl-amino]-methyl)-phenyl)-1-(4-methoxy-phenyl)-propenone

15

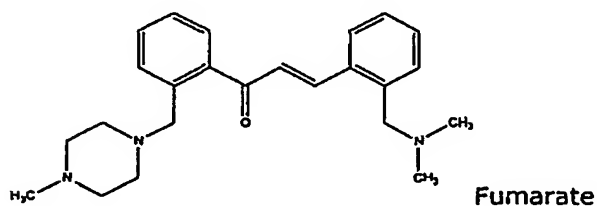


General procedure I gave the title compound as yellow crystals in 45% yield

¹H-NMR (DMSO) δ 8.12 (d, 2H), 7.90 (d, 1H), 7.77 (s, 1H), 7.74-7.72 (m, 1H), 7.64 (d, 1H), 7.37 (d, 2H), 7.04 (d, 2H), 6.51 (s, 4H), 3.82 (s, 3H), 3.55 (s, 2H), 3.01 (t, 2H), 2.62 (t, 2H), 2.57 (s, 6H), 2.13 (s, 3H)

II-113 (*E*)-3-(2-Dimethylaminomethyl-phenyl)-1-[2-(4-methyl-piperazin-1-ylmethyl)-phenyl]-propenone

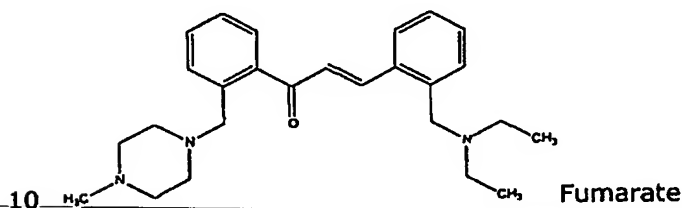
25



General procedure F gave the title compound as pale brown crystals in 44% yield

¹H-NMR (DMSO) δ 7.90-7.87 (m, 1H), 7.61 (d, 1H), 7.44-7.36 (m, 6H), 7.26-7.24 (m, 1H), 7.00 (d, 1H), 6.57 (s, 3H), 3.58 (s, 2H), 3.28 (s, 2H), 2.40 (br, 4H), 2.32 (br, 4H), 5 2.20 (s, 3H), 1.95 (s, 6H)

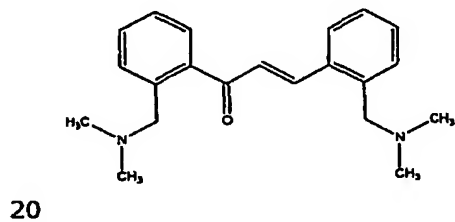
II-114 (*E*)- 3-(2-Diethylaminomethyl-phenyl)-1-[2-(4-methyl-piperazin-1-ylmethyl)-phenyl]-propenone



General procedure F gave the title compound as white crystals in 44% yield

¹H-NMR (DMSO) δ 7.90 (dd, 1H), 7.77 (d, 1H), 7.43-7.27 (m, 7H), 7.00 (d, 1H), 6.59 (s, 15 3H), 3.55 (s, 2H), 3.37 (s, 2H), 2.30 (br, 8H), 2.27 (q, 4H), 2.19 (s, 3H), 1.09 (t, 6H)

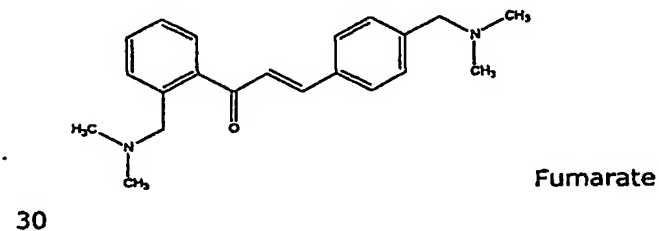
II-115 (*E*)- 1,3-Bis-(2-dimethylaminomethyl-phenyl)-propenone



General procedure F gave the title compound as brown oil in 37% yield

¹H-NMR(300 MHz, CDCl₃) δ 7.71-7.68 (m, 1H), 7.67 (d, 1H), 7.41-7.20 (m, 7H), 6.93 (d, 1H), 3.57 (s, 2H), 3.29 (s, 2H), 2.11 (s, 6H), 2.03 (s, 6H)

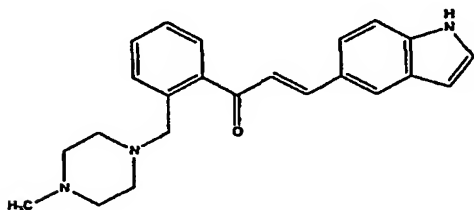
25 **II-116** (*E*)- 3-(4-Dimethylaminomethyl-phenyl)-1-(2-dimethylaminomethyl-phenyl)-propenone



General procedure F gave the title compound as white crystals in 39% yield

¹H-NMR (DMSO) δ 7.73 (d, 2H), 7.55-7.42 (m, 4H), 7.39 (d, 2H), 7.32 (s, 2H), 6.59 (s, 4H), 3.65 (s, 4H), 2.29 (s, 6H), 2.14 (s, 6H)

5 **II-117** (E)- 3-(1H-Indol-5-yl)-1-[2-(4-methyl-piperazin-1-ylmethyl)-phenyl]-propenone

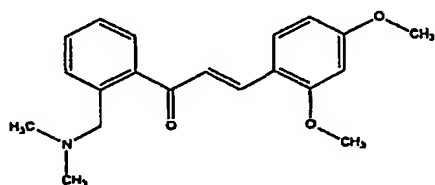


General procedure F gave the title compound as yellow crystals in 13% yield

10

¹H-NMR (DMSO) δ 11.33 (s, 1H), 7.85 (s, 1H), 7.50 (dd, 1H), 7.47-7.35 (m, 7H), 7.09 (d, 1H), 6.47 (t, 1H), 3.54 (s, 2H), 2.26 (br, 4H), 2.15 (br, 4H), 2.00 (s, 3H)

15 **II-118** (E)- 3-(2,4-Dimethoxy-phenyl)-1-(2-dimethylaminomethyl-phenyl)-propenone

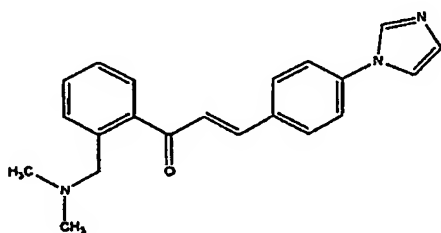


Fumarate

General procedure F gave the title compound as yellow crystals in 32% yield

20 ¹H-NMR (DMSO) δ 7.75 (d, 1H), 7.63 (d, 1H), 7.57-7.42 (m, 4H), 7.21 (d, 1H), 6.63-6.58 (m, 3H), 6.60 (s, 2H), 3.84 (s, 3H), 3.83 (s, 3H), 3.69 (s, 2H), 2.22 (s, 6H)

II-119 (E)- 1-(2-Dimethylaminomethyl-phenyl)-3-(4-imidazol-1-yl-phenyl)-propenone



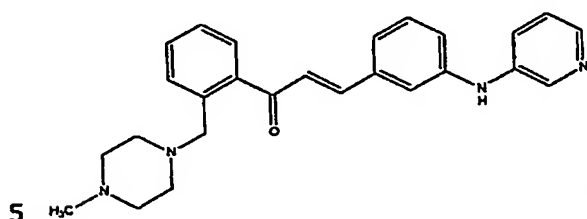
25

Fumarate

General procedure F gave the title compound as pale yellow powder in 17% yield

30 ¹H-NMR (DMSO) δ 8.38 (t, 1H), 7.92 (d, 2H), 7.85 (t, 1H), 7.74 (d, 2H), 7.56-7.43 (m, 4H), 7.38 (s, 2H), 7.13 (t, 1H), 6.61 (s, 2H), 3.65 (s, 2H), 2.14 (s, 6H)

II-120• (*E*)-1-[2-(4-Methyl-piperazin-1-ylmethyl)-phenyl]-3-[3-(pyridin-3-ylamino)-phenyl]-propenone

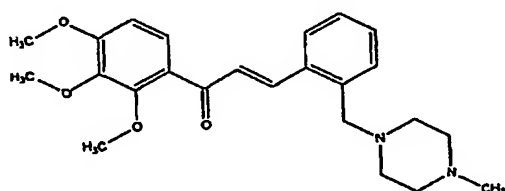


Oxalate

General procedure F gave the title compound as yellow crystals in 38% yield

¹H-NMR (DMSO) δ 8.55 (br, 1H), 8.38 (d, 1H), 8.06 (t, 1H), 7.54-7.13 (m, 12H), 3.67 (under H₂O, 2H), 2.90 (br, 8H), 2.66 (s, 3H)

II-121 (*E*)-3-[2-(4-Methyl-piperazin-1-ylmethyl)-phenyl]-1-(2,3,4-trimethoxy-phenyl)-propenone

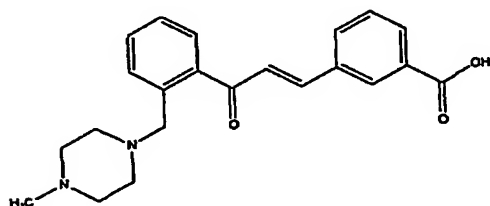


Fumarate

General procedure F gave the title compound as off-white crystals in 14% yield

¹H-NMR (DMSO) δ 8.00 (d, 1H), 7.83 (dd, 1H), 7.44-7.31 (m, 4H), 7.24 (d, 1H), 6.93 (d, 1H), 6.59 (s, 4H), 3.87 (s, 3H), 3.82 (s, 3H), 3.79 (s, 3H), 3.53 (s, 2H), 2.5 (br, under DMSO, 4H), 2.39 (br, 4H), 2.32 (s, 3H)

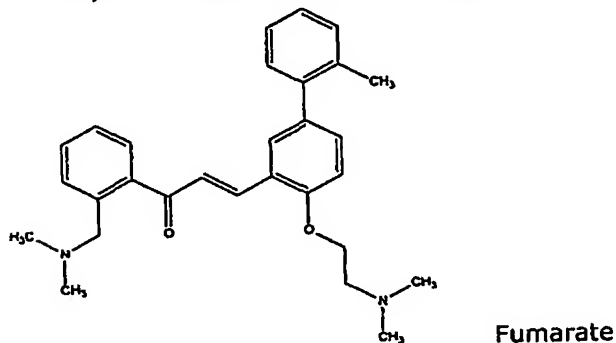
II-122. (*E*)-3-{3-[2-(4-Methyl-piperazin-1-ylmethyl)-phenyl]-3-oxo-propenyl}-benzoic acid



General procedure F gave the title compound as brown crystals in 57% yield

¹H-NMR (DMSO) δ 8.15 (s, 1H), 7.93 (t, 2H), 7.49 (t, 1H), 7.52-7.37 (m, 4H), 7.30 (d, 1H), 7.21 (d, 1H), 3.55 (s, 2H), 2.26 (br, 4H), 2.20 (br, 4H), 2.05 (s, 3H)

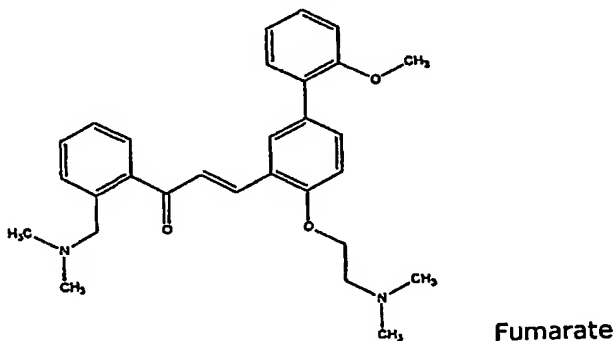
II-123 (*E*)-3-[4-(2-Dimethylamino-ethoxy)-2'-methyl-biphenyl-3-yl]-1-(2-dimethylaminomethyl-phenyl)-propenone



General procedure F gave the title compound as pale green crystals in 28% yield

¹H-NMR (DMSO) δ 7.79 (d, 1H), 7.69 (d, 1H), 7.55-7.37 (m, 5H), 7.28-7.22 (m, 5H), 7.16 (d, 1H), 6.59 (s, 4H), 4.24 (t, 2H), 3.67 (s, 2H), 2.87 (t, 2H), 2.32 (s, 6H), 2.26 (s, 3H), 2.17 (s, 6H)

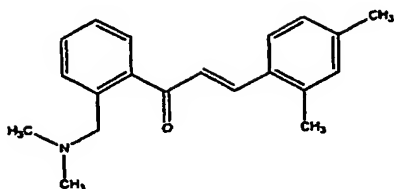
II-124 (*E*)-3-[4-(2-Dimethylamino-ethoxy)-2'-methoxy-biphenyl-3-yl]-1-(2-dimethylaminomethyl-phenyl)-propenone



General procedure F gave the title compound as pale green crystals in 29% yield

¹H-NMR (DMSO) δ 7.86 (d, 1H), 7.68 (d, 1H), 7.55-7.43 (m, 5H), 7.37-7.31 (m, 3H), 7.12 (t, 2H), 7.05 (t, 1H), 6.58 (s, 4H), 4.25 (t, 2H), 3.76 (s, 3H), 3.68 (s, 2H), 2.91 (t, 2H), 2.34 (s, 6H), 2.19 (s, 6H)

II-125 (*E*)-1-(2-Dimethylaminomethyl-phenyl)-3-(2,4-dimethyl-phenyl)-propenone



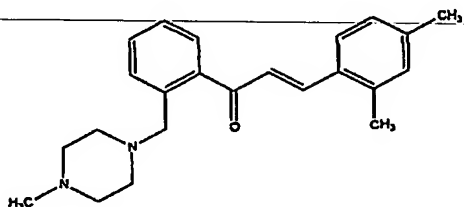
Fumarate

General procedure F gave the title compound as white crystals in 50% yield

- 5 $^1\text{H-NMR}$ (DMSO) δ 7.75 (d, 1H), 7.61-7.56 (m, 2H), 7.50-7.45 (m, 3H), 7.19 (d, 1H), 7.22-7.07 (m, 2H), 6.59 (s, 2H), 3.70 (s, 2H), 2.29 (s, 3H), 2.28 (s, 3H), 2.20 (s, 6H)

II-126 (E)-3-(2,4-Dimethyl-phenyl)-1-[2-(4-methyl-piperazin-1-ylmethyl)-phenyl]-propenone

10

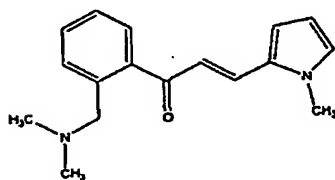


Fumarate

General procedure F gave the title compound as off-white crystals in 32% yield

- 15 $^1\text{H-NMR}$ (DMSO) δ 7.72 (d, 1H), 7.50 (d, 1H), 7.46-7.39 (m, 4H), 7.11-7.06 (m, 3H), 6.59 (s, 4H), 3.60 (s, 2H), 2.5 (under DMSO, 4H), 2.37 (br, 4H), 2.29 (s, 6H), 2.26 (s, 3H)

II-127 (E)-1-(2-Dimethylaminomethyl-phenyl)-3-(1-methyl-1H-pyrrol-2-yl)-propenone



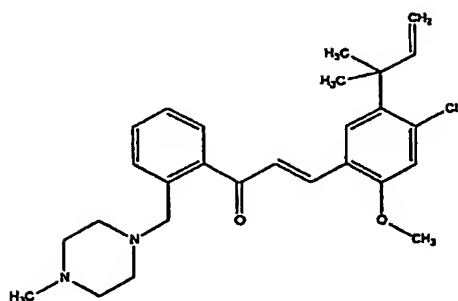
20

Fumarate

General procedure F gave the title compound as brown crystals in 22% yield

- 25 $^1\text{H-NMR}$ (DMSO) δ 7.57-7.40 (m, 4H), 7.39 (d, 1H), 7.07 (t, 1H), 6.99 (d, 1H), 6.92 (dd, 1H), 6.59 (s, 2H), 6.16 (dd, 1H), 3.68 (br, 6H), 2.21 (s, 6H)

II-128 (E)-3-[4-Chloro-5-(1,1-dimethyl-allyl)-2-methoxy-phenyl]-1-[2-(4-methyl-piperazin-1-ylmethyl)-phenyl]-propenone

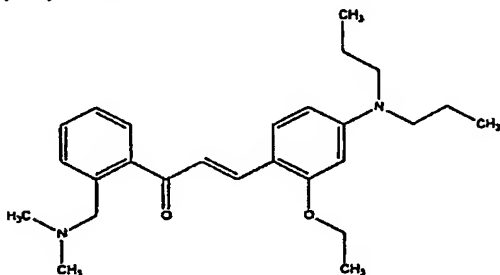


Fumarate

General procedure F gave the title compound as orange crystals in 25% yield

5 $^1\text{H-NMR}$ (300 MHz, DMSO-d_6) δ 7.68 (s, 1H), 7.46-7.37 (m, 5H), 7.18 (d, 1H), 7.11 (s, 1H), 6.59 (s, 4H), 6.13-6.04 (dd, 1H), 5.04-5.00 (dd, 1H), 4.94-4.88 (dd, 1H), 3.83 (s, 3H), 3.56 (s, 2H), 2.60-2.25 (m, 8H), 2.23 (s, 3H), 1.49 (s, 6H)

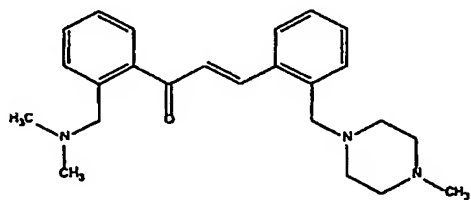
II-129• (E)- 1-(2-Dimethylaminomethyl-phenyl)-3-(4-dipropylamino-2-ethoxy-phenyl)-
10 propenone



(E)-3-(4-Dibutylamino-2-fluoro-phenyl)-1-(2-dimethylaminomethyl-phenyl)-propenone (4
mmol), was stirred in 0.1 M sodium ethanolate in EtOH (50 mL) at 25 °C overnight. The
15 solution was evaporated on Celite® and purified by flash chromatography to give the title
compound as brown oil in 0.9% yield

$^1\text{H-NMR}$ (300 MHz, CDCl_3) δ 7.59 (d, 1H), 7.49 (d, 1H), 7.40-7.34 (m, 3H), 7.29 (dd,
1H), 6.96 (d, 1H), 6.23 (dd, 1H), 6.05 (d, 1H), 4.00 (q, 2H), 3.56 (s, 2H), 3.27 (t, 4H),
20 2.17 (s, 6H), 1.68-1.57 (m, 4H), 1.36 (t, 3H), 0.94 (t, 6H)

II-130 (E)-1-(2-Dimethylaminomethyl-phenyl)-3-[2-(4-methyl-piperazin-1-ylmethyl)-
phenyl]-propenone

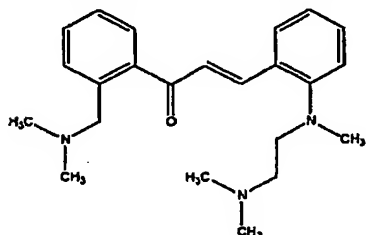


25 Fumarate

General procedure F gave the title compound as brown crystals in 1% yield

$^1\text{H-NMR}$ (300 MHz, DMSO-d_6) δ 7.89-7.86 (m, 1H), 7.70 (d, 1H), 7.46-7.34 (m, 6H), 7.27-7.24 (m, 1H), 7.00 (d, 1H), 6.60 (s, 4H), 3.53 (s, 2H), 3.35 (s, 2H), 2.5 (under DMSO, 4H), 2.20 (br, 4H), 2.20 (s, 3H), 2.08 (s, 6H)

II-131. (*E*)-3-{2-[(2-Dimethylamino-ethyl)-methyl-amino]-phenyl}-1-(2-dimethylaminomethyl-phenyl)-propenone



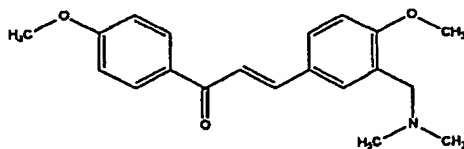
10

General procedure F gave the title compound as green oil in 39% yield

$^1\text{H-NMR}$ (300 MHz, CDCl_3) δ 7.67 (d, 1H), 7.62 (dd, 1H), 7.44-7.41 (m, 3H), 7.39-7.31 (m, 2H), 7.11-7.03 (m, 2H), 7.03 (d, 1H), 3.56 (s, 2H), 3.03 (t, 2H), 2.71 (s, 3H), 2.36 (t, 2H), 2.17 (s, 12 H)

15

II-132. (*E*)-3-(3-Dimethylaminomethyl-4-methoxy-phenyl)-1-(4-methoxy-phenyl)-propenone



20

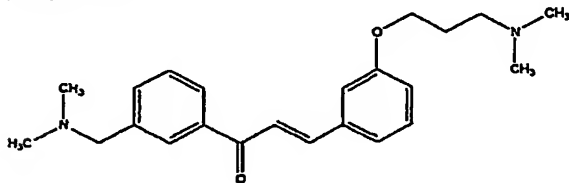
Fumarate

General procedure F gave the title compound as slightly yellow crystals in 38% yield

$^1\text{H-NMR}$ (300 MHz, DMSO-d_6) δ 8.13 (d, 2H), 7.90 (d, 1H), 7.83 (dd, 1H), 7.78 (d, 1H), 7.67 (d, 1H), 7.10 (t, 3H), 6.58 (s, 2H), 3.87 (s, 6H), 3.74 (s, 2H), 2.38 (s, 6H)

25

II-133. (*E*)-1-(3-Dimethylaminomethyl-phenyl)-3-[3-(3-dimethylamino-propoxy)-phenyl]-propenone



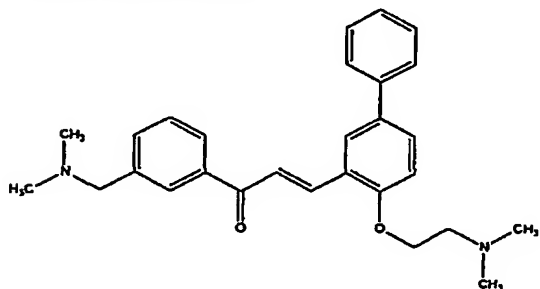
30

General procedure F gave the title compound as yellow oil in 38% yield

¹H NMR (CDCl₃) δ 7.97-7.92 (m, 2H), 7.79 (d, 1H), 7.59-7.57 (m, 2H), 7.49 (t, 1H), 7.34 (t, 1H), 7.26-7.20 (m, 2H), 6.98 (dd, 1H), 4.09 (t, 2H), 3.53 (s, 2H), 2.51 (t, 2H), 2.30 (s, 6H), 2.29 (s, 6H), 2.01 (m, 2H)

5

II-134 (*E*)-3-[4-(2-Dimethylamino-ethoxy)-biphenyl-3-yl]-1-(3-dimethylaminomethyl-phenyl)-propenone

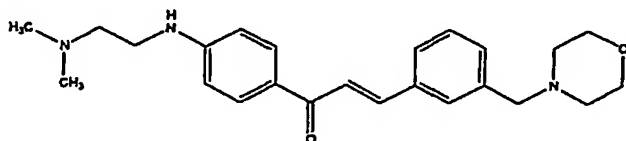


10 General procedure F gave the title compound as yellow oil in 42% yield

¹H NMR (CDCl₃) δ 8.07 (d, 1H), 7.90-7.88 (m, 2H), 7.77 (d, 1H), 7.71 (d, 1H), 7.54-7.47 (m, 4H), 7.41-7.38 (m, 3H), 7.36-7.25 (m, 1H), 6.96 (d, 1H), 4.15 (t, 2H), 3.44 (s, 2H), 2.80 (t, 2H), 2.31 (s, 6H), 2.20 (s, 6H)

15

II-135 (*E*)-1-[4-(2-Dimethylamino-ethylamino)-phenyl]-3-(3-morpholin-4-ylmethyl-phenyl)-propenone



Fumarate

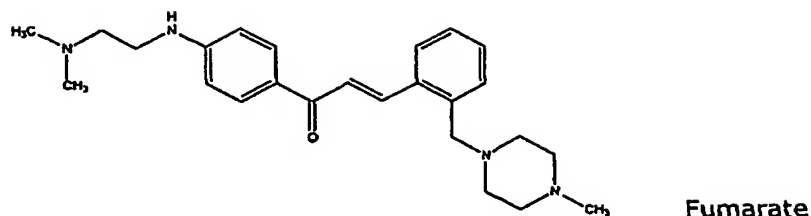
20

General procedure F gave the title compound as yellow crystals in 37% yield

¹H NMR (DMSO) δ 7.99 (d, 2H), 7.88 (d, 1H), 7.75-7.72 (m, 2H), 7.61 (d, 1H), 7.43-7.36 (m, 2H), 6.74-6.71 (m, 3H), 6.57 (s, 1H), 3.58 (t, 2H), 3.51 (s, 2H), 3.31 (q, 2H), 2.67 (t, 2H), 2.39-2.36 (m, 10H)

25

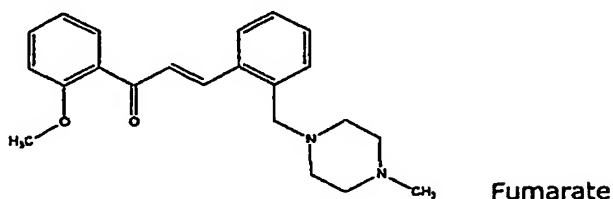
II-136 (*E*)-1-[4-(2-Dimethylamino-ethylamino)-phenyl]-3-[2-(4-methyl-piperazin-1-ylmethyl)-phenyl]-propenone



General procedure F gave the title compound as yellow crystals in 11% yield

- 5 ^1H NMR (DMSO) δ 7.93 (d, 1H), 7.85-7.81 (m, 3H), 7.58 (d, 1H), 7.25-7.21 (m, 3H), 6.63 (bs, 1H), 6.55 (d, 2H), 6.45 (s, 5H), 3.47 (s, 2H), 3.22 (q, 2H), 2.66 (t, 2H), 2.45 (bs, 2H), 2.32 (s, 6H), 2.20 (s, 3H)

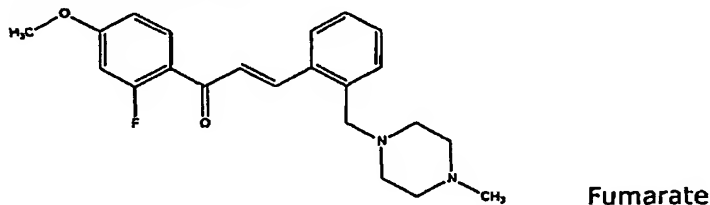
10 **II-137** (*E*)-1-(2-Methoxy-phenyl)-3-[2-(4-methyl-piperazin-1-ylmethyl)-phenyl]-propenone



General procedure F gave the title compound as slightly yellow crystals in 3% yield

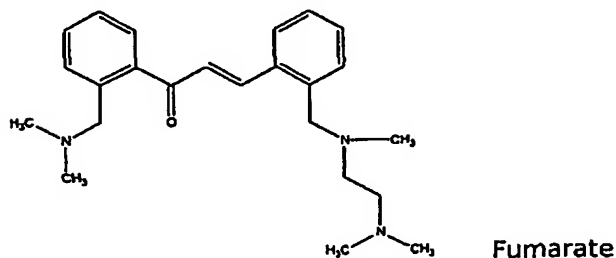
- 15 ^1H -NMR(300 MHz, DMSO- d_6) δ 7.92 (d, 1H), 7.84-7.81 (m, 1H), 7.55-7.49 (m, 1H), 7.43 (dd, 1H), 7.38-7.28 (m, 3H), 7.19 (d, 1H), 7.15 (d, 1H), 7.06 (td, 1H), 6.60 (s, 4H), 3.84 (s, 3H), 3.45 (s, 2H), 2.5 (under DMSO, 4H), 2.30 (br, 4H), 2.24 (s, 3H)

20 **II-138** (*E*)-1-(2-Fluoro-4-methoxy-phenyl)-3-[2-(4-methyl-piperazin-1-ylmethyl)-phenyl]-propenone



General procedure F gave the title compound as slightly yellow crystals in 15% yield

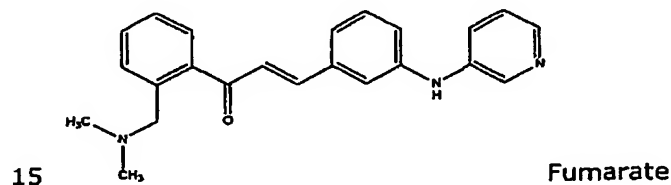
- 25 ^1H -NMR(300 MHz, DMSO- d_6) δ 8.12 (d, 1H), 7.87-7.77 (m, 2H), 7.40-7.29 (m, 4H), 7.01-6.91 (m, 2H), 6.60 (s, 3H), 3.87 (s, 3H), 3.56 (s, 2H), 2.5 (under DMSO, 4H), 2.41 (br, 4H), 2.28 (s, 3H)
-

II-139 (*E*)-3-(2-[[2-(2-Dimethylamino-ethyl)-methyl-amino]-methyl]-phenyl)-1-(2-dimethylaminomethyl-phenyl)-propenone

5

General procedure F gave the title compound as pale brown crystals in 4% yield

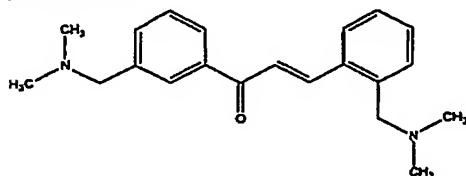
¹H-NMR(300 MHz, DMSO-d₆) δ 7.91-7.88 (m, 1H), 7.75 (d, 1H), 7.50-7.33 (m, 7H), 7.13 (d, 1H), 6.57 (s, 6H), 3.62 (s, 2H), 3.48 (s, 2H), 2.79 (t, 2H), 2.5 (under DMSO, 2H), 2.46 (s, 6H), 2.12 s, 6H), 2.00 (s, 3H)

II-140 (*E*)-1-(2-Dimethylaminomethyl-phenyl)-3-[3-(pyridin-3-ylamino)-phenyl]-propenone

15

General procedure F gave the title compound as yellow crystals in 7% yield

¹H-NMR(300 MHz, DMSO-d₆) δ 8.46 (s, 1H), 8.36 (d, 1H), 8.06 (dd, 1H), 7.64-7.13 (m, 11H), 6.60 (s, 3H), 3.65 (s, 2H), 2.16 (s, 6H)

II-141 (*E*)-3-(2-Dimethylaminomethyl-phenyl)-1-(3-dimethylaminomethyl-phenyl)-propenone

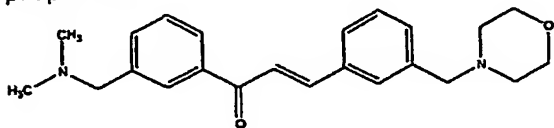
25

General procedure F gave the title compound as brown oil in 48% yield

¹H NMR (CDCl₃) δ 8.30 (d, 1H), 7.97-7.94 (m, 2H), 7.79-7.76 (m, 1H), 7.58 (d, 1H), 7.50-7.45 (m, 2H), 7.38-7.35 (m, 3H), 3.55 (s, 2H), 3.53 (s, 2H), 2.29 (s, 6H), 2.26 (s, 6H)

30

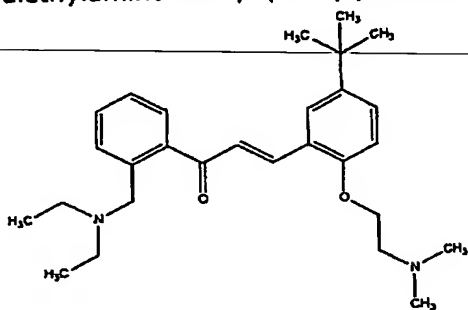
II-142 (*E*)-1-(3-Dimethylaminomethyl-phenyl)-3-(3-morpholin-4-ylmethyl-phenyl)-propenone



5 General procedure F gave the title compound as yellow oil in 26% yield

^1H NMR (CDCl_3) δ 7.98-7.94 (m, 2H), 7.84 (d, 1H), 7.64-7.28 (m, 7H), 3.75 (t, 4H), 3.56 (s, 2H), 3.55 (s, 2H), 2.49 (t, 4H), 2.30 (s, 6H)

10 **II-143** (*E*)-3-[5-tert-Butyl-2-(2-dimethylamino-ethoxy)-phenyl]-1-(2-diethylaminomethyl-phenyl)-propenone

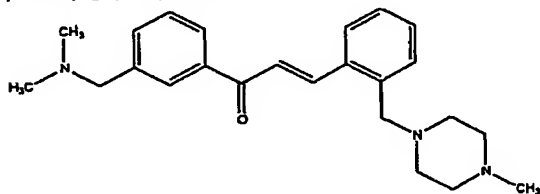


General procedure F gave the title compound as green oil in 42% yield

15

^1H -NMR (DMSO) δ 7.68 (d, 1H), 7.52 (d, 1H), 7.43-7.32 (m, 5H), 7.20 (d, 1H), 6.98 (d, 1H), 4.04 (t, 2H), 3.59 (s, 2H), 2.54 (t (under DMSO), 2H), 2.33 (q, 4H), 2.08 (s, 6H), 1.28 (s, 9H), 0.82 (t, 6H)

20 **II-144** (*E*)-1-(3-Dimethylaminomethyl-phenyl)-3-[2-(4-methyl-piperazin-1-ylmethyl)-phenyl]-propenone

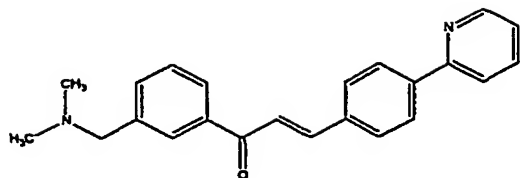


General procedure F gave the title compound as brown oil in 18% yield

25

^1H NMR (DMSO) δ 8.31 (d, 1H), 7.94-7.91 (m, 2H), 7.75-7.72 (m, 1H), 7.55 (d, 1H), 7.48-7.39 (m, 2H), 7.33 (dd, 3H), 7.26 (s, 2H), 3.60 (s, 2H), 3.51 (s, 2H), 2.52-2.33 (bs, 4H), 2.26 (s, 6H), 2.25 (s, 3H)

30 **II-145** (*E*)-1-(3-Dimethylaminomethyl-phenyl)-3-(4-pyridin-2-yl-phenyl)-propenone



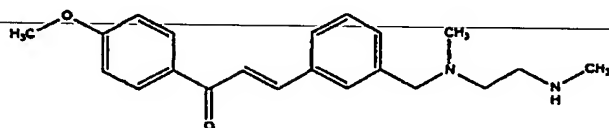
Fumarate

General procedure F gave the title compound as slightly yellow crystals in 3% yield

- 5 ^1H NMR (DMSO) δ 8.70 (d, 1H), 8.21-7.98 (m, 8H), 7.92 (d, 1H), 7.81 (d, 1H), 7.66 (d, 1H), 7.57 (t, 1H), 3.39 (dd, 1H), 6.60 (s, 2H), 3.74 (s, 2H), 2.32 (s, 6H)

II-146. (E)-1-(4-Methoxy-phenyl)-3-(3-([methyl-(2-methylamino-ethyl)-amino]-methyl)-phenyl)-propenone

10

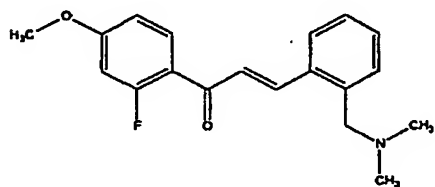


General procedure I gave the title compound as slightly yellow crystals in 34% yield

- 15 ^1H NMR (CDCl_3) δ 8.05 (d, 2H), 7.80 (d, 1H), 7.75 (s, 1H), 7.61-7.57 (m, 1H), 7.56 (d, 1H), 7.48-7.37 (m, 2H), 6.98 (d, 2H), 3.89 (s, 3H), 3.56-3.40 (m, 2H), 3.31 (s, 2H), 2.62-2.56 (m, 2H), 2.20 (s, 9H)

II-147 (E)-3-(2-Dimethylaminomethyl-phenyl)-1-(2-fluoro-4-methoxy-phenyl)-propenone

20



Fumarate

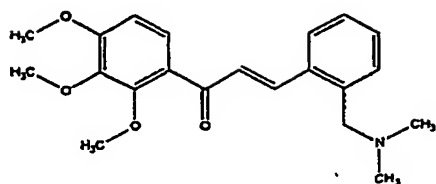
General procedure F gave the title compound as slightly yellow crystals in 12% yield

25

- ^1H NMR (DMSO) δ 8.10 (d, 1H), 7.98-7.80 (m, 2H), 7.40-7.31 (m, 4H), 7.01-6.92 (m, 2H), 6.59 (s, 3H), 3.87 (s, 3H), 3.50 (s, 2H), 2.14 (s, 6H)

II-148 (E)-3-(2-Dimethylaminomethyl-phenyl)-1-(2,3,4-trimethoxy-phenyl)-propenone

30



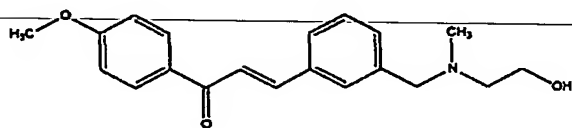
Fumarate

General procedure F gave the title compound as white crystals in 17% yield

- 5 ^1H NMR (DMSO) δ 7.99 (d, 1H), 7.85-7.82 (m, 1H), 7.49-7.28 (m, 5H), 6.94 (d, 1H), 6.59 (s, 4H), 3.87 (s, 3H), 3.83 (s, 3H), 3.78 (s, 3H), 3.46 (s, 2H), 2.11 (s, 3H)

II-149 (E)-3-(3-((2-Hydroxy-ethyl)-methyl-amino)-methyl)-phenyl-1-(4-methoxy-phenyl)-propenone

10



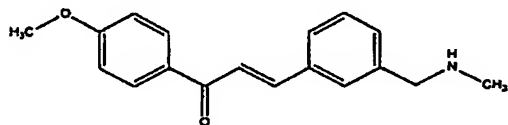
Fumarate

General procedure F gave the title compound as pale yellow crystals in 16% yield

- 15 ^1H NMR (DMSO) δ 8.17 (d, 2H), 7.93 (d, 1H), 7.84 (s, 1H), 7.78-7.76 (m, 1H), 7.70 (d, 1H), 7.42 (d, 2H), 7.09 (d, 2H), 6.59 (s, 2H), 3.87 (s, 3H), 3.66 (s, 2H), 3.56 (t, 2H), 2.54 (t, 2H), 2.26 (s, 3H)

II-150 (E)-1-(4-Methoxy-phenyl)-3-(3-methylaminomethyl-phenyl)-propenone

20

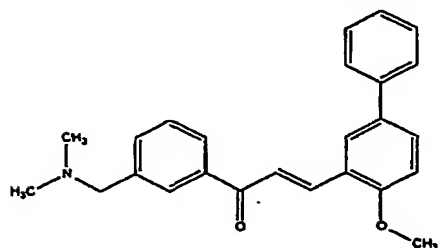


Fumarate

General procedure F gave the title compound as yellow crystals in 18% yield

- 25 ^1H NMR (DMSO) δ 8.15 (d, 2H), 8.04 (s, 1H), 7.95 (d, 1H), 7.80 (d, 1H), 7.69 (d, 1H), 7.52-7.47 (m, 2H), 7.09 (d, 2H), 6.51 (s, 2H), 4.04 (s, 2H), 3.87 (s, 3H), 2.48 (s, 3H)

II-151 (E)-1-(3-Dimethylaminomethyl-phenyl)-3-(4-methoxy-biphenyl-3-yl)-propenone

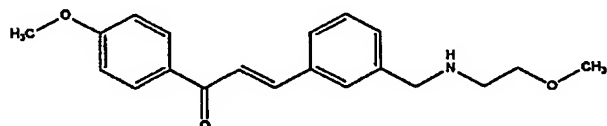


General procedure F gave the title compound as yellow crystals in 37% yield

¹H NMR (CDCl₃) δ 8.17 (d, 1H), 7.94-7.91 (m, 2H), 7.86 (d, 1H), 7.67 (d, 1H), 7.63-7.57 (m, 4H), 7.55-7.43 (m, 3H), 7.35 (t, 1H), 7.03 (d, 1H), 3.96 (s, 3H), 3.51 (s, 2H), 2.27 (s, 6H)

II-152 (E)-3-{3-[(2-Methoxy-ethylamino)-methyl]-phenyl}-1-(4-methoxy-phenyl)-propenone

10



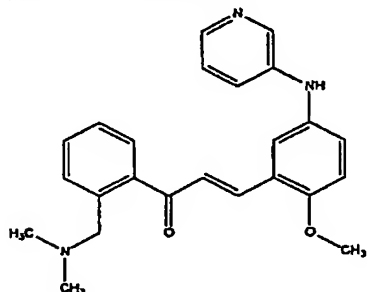
Fumarate

General procedure F gave the title compound as white crystals in 63% yield

¹H NMR (DMSO) δ 8.15 (d, 2H), 7.97 (s, 1H), 7.94 (d, 1H), 7.80 (d, 1H), 7.70 (d, 1H), 7.49-7.45 (m, 2H), 7.10 (d, 2H), 6.55 (s, 2H), 3.99 (s, 2H), 3.87 (s, 3H), 3.52 (t, 2H), 3.26 (s, 3H), 2.88 (t, 2H)

II-153 (E)-1-(2-Dimethylaminomethyl-phenyl)-3-[2-methoxy-5-(pyridin-3-ylamino)-phenyl]-propenone

20

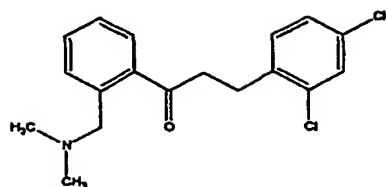


General procedure F gave the title compound as yellow crystals in 35% yield

¹H NMR (CDCl₃) δ 8.29 (dd, 1H), 8.13 (dd, 1H), 7.56 (d, 1H), 7.43-7.33 (m, 5H), 7.28-7.22 (m, 1H), 7.18-7.14 (m, 2H), 7.10 (d, 1H), 6.90 (d, 1H), 5.60 (s, 1H), 3.85 (s, 3H), 3.57 (s, 2H), 2.16 (s, 6H)

II-154 3-(2,4-Dichloro-phenyl)-1-(2-dimethylaminomethyl-phenyl)-propanone

30



Fumarate

Triethylsilane (0.150 mol) was added to a solution of 3-(2,4-Dichloro-phenyl)-1-(2-dimethylaminomethyl-phenyl)-propenone (0.0075 mol) in trifluoro acetic acid stirred at 25 °C for 30 hours, before the solution was poured into ice-cold NaOH (2M, 150 mL). Extracted with EtOAc, dried over Na₂SO₄, filtered and evaporated on Celite®. Purified by flash chromatography (EtOAc/heptane, 3% Et₃N). The resulting oil was dissolved in MeOH/Et₂O (1:9 v/v, 10 mL) and a solution of fumaric acid in MeOH/Et₂O (1:9 v/v) was added. The title compound was isolated as white crystals in 24% yield (614 mg).

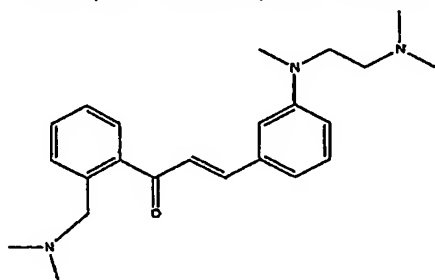
10

The purity was >95% determined by HPLC.

¹H-NMR (DMSO) δ 12.96 (br, 1H), 7.58-7.35 (m, 7H), 6.60 (s, 2H), 3.57 (s, 2H), 3.16 (t, 2H), 3.00 (t, 2H), 2.14 (s, 6H).

15

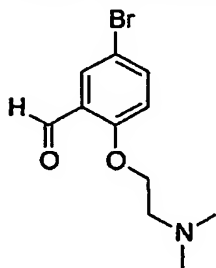
II-155 (E)-3-{3-[(2-Dimethylamino-ethyl)-methyl-amino]-phenyl}-1-(2-dimethylaminomethyl-phenyl)-propenone



Fumarate

General procedure F gave the fumarate salt of title compound as yellow crystals in 42 % yield.

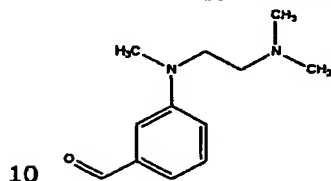
¹H-NMR(300 MHz, DMSO-d₆) δ 7.54-7.38 (m, 4H), 7.27 (s, 2H), 7.22 (t, 1H), 7.05-6.98 (m, 2H), 6.81 (dd, 1H), 6.58 (s, 4H), 3.61 (s, 2H), 3.59 (t, 2H), 2.93 (s, 3H), 2.78 (t, 2H), 2.48 (s, 6H), 2.13 (s, 6H).

II-156 5-Bromo-2-(2-dimethylamino-ethoxy)-benzaldehyde

General procedure E gave the title compound as a yellow oil in 65 % yield

5

^1H NMR (CDCl_3) δ 10.43 (s, 1H), 7.94 (d, 1H), 7.63 (dd, 1H), 6.92 (d, 1H), 4.19 (t, 2H), 2.81 (t, 2H), 2.37 (s, 6H)

II-157 3-[(2-Dimethylamino-ethyl)-methyl-amino]-benzaldehyde

10

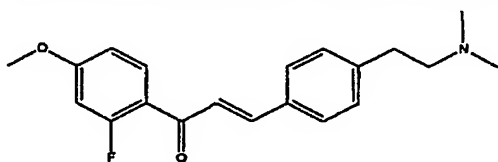
General procedure D gave the title compound as yellow oil in 90% yield

^1H -NMR(300 MHz, CDCl_3) δ 9.91 (s, 1H), 7.35 (t, 1H), 7.12-7.05 (m, 2H), 7.00-6.93 (dd, 1H), 3.56 (t, 2H), 3.05 (s, 3H), 2.55 (t, 2H), 2.38 (s, 6H)

15

II-158

3-[4-(2-Dimethylamino-ethyl)-phenyl]-1-(2-fluoro-4-methoxy-phenyl)-propenone



20

Fumarate

General procedure F gave the title compound as yellow crystals in 61% yield

^1H -NMR(300 MHz, $\text{DMSO}-d_6$) δ 7.83 (t, 1H), 7.62 (d, 2H), 7.63 (d, 1H), 7.47 (dd, 1H), 7.32 (d, 2H), 7.05-6.90 (m, 2H), 6.56 (s, 1H, fumarat), 3.87 (s, 3H), 2.90-2.68 (m, 4H), 2.39 (s, 6H)

25

Determination of metabolic stability

Incubations were performed with Wistar rat liver microsomes (0.5 mg/ml) in 2% sodium bicarbonate solution. NADP (0.15 mg/ml), glucose-6-phosphate (0.5 mg/ml) and glucose-6-phosphate dehydrogenase (0.38 units/ml) were used as NADPH generation system and UDPGA (0.48 mg/ml) was added to include the phase II reaction, glucuronic acid

5 conjugation, in the assay. After 5 minutes of pre-incubation the reaction was started by addition of the test article to give a final concentration of 10 µM. Samples were incubated for 30 min at 37°C and the reactions were terminated by addition of equal volumes of acetonitrile. Blank incubations were performed at the same concentration but without addition of microsomes.

10

The fraction of compound metabolised during the 30 min incubation was determined quantitatively by HPLC with UV detection using a Waters Alliance 2690 separation module and the Waters 996 PDA-detector, Waters corp, Milford, USA. Samples were analysed on a XTerra RP₈ column (5 µm) 4.6 x 150 mm (Waters corp, Milford, USA) with a linear gradient elution system. Initial conditions were 40% mobile phase A (acetonitrile) and 60% mobile phase B (10 mM ammonium acetate pH 9.5). During the first 20 minutes runtime, the mobile phase was changed to 90% A and 10% B followed by a fast 5 minutes gradient to return to initial conditions and a 5 minutes equilibration time. The flow rate was 1 ml/min and injection volume 50 µl.

20

Determination of solubility

Solubility of the compounds was determined in 1M phosphate buffer pH 7.4 by preparation of suspensions in brown glass tubes. The suspensions were rotated slowly for 24 hours.

25 Aliquots were centrifuged for 10 minutes at 10 000 rpm, supernatants were diluted in 50% acetonitrile prior to HPLC analysis and the concentrations in the samples were quantified against a standard curve. The concentration of the compound in the supernatant is used as term of solubility. The HPLC method used for the assessment of solubility is the same as used in the in vitro metabolism assay.

30

Biological testing

General methods

***In vitro* microbiological testing**

35

MIC determination in broth microdilution assay

Compounds were screened for activity against a panel of 10 different non-fastidious bacteria growing aerobically (*Staphylococcus aureus* ATCC29213, *Staphylococcus aureus* ATCC33591, *Staphylococcus intermedius* #2357 (clinical isolate from the Copenhagen area), *Enterococcus faecalis* ATCC29212, *Enterococcus faecium* #17501 (vancomycin-resistant clinical isolate), *Streptococcus pneumoniae* #998 (clinical isolate), *Streptococcus pyogenes* #14813 (clinical isolate), *Streptococcus agalactiae* #19855 (clinical isolate),

40

- Escherichia coli* ATCC25922 and *Escherichia coli* ESS) The screening assay was done in 200 µl MH-broth cultures in microtitre plates For compounds exhibiting activity in the initial screen MIC was determined in a microdilution assay using MH-broth as described by NCCLS (National Committee for Clinical Laboratory Standards Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically, Approved Standard – Fifth Edition M7-A5 NCCLS 2000) modified to include uninoculated dilution series of test compounds to facilitate MIC determination if the test compound should precipitate MIC was determined as the lowest concentration of test compound able to inhibit visible growth of bacteria MICs for ATCC type strains fell within the limits posted by the NCCLS (National Committee for Clinical Laboratory Standards Performance Standards for Antimicrobial Susceptibility Testing, Eleventh Informational Supplement M100-S11 NCCLS 2001) when tested against vancomycin, tetracycline, gentamycin

MIC and MBC determination in broth macrodilution assay

- MIC and MBC of test compounds were determined in a broth macrodilution assay using 2 ml MH-broth cultures and an inoculum of approximately 5×10^5 CFU/ml as described by Amsterdam (Amsterdam, D Susceptibility testing of antimicrobials in liquid media In V Lorian (ed) Antibiotics in Laboratory Medicine 4 edition Williams & Wilkins 1996) MIC was determined as the minimal concentration of test compound able to inhibit visible growth of bacteria Samples from cultures inhibited by test compound were plated onto unselective blood agar plates MBC was determined as the minimal concentration of test compound able to decrease colony count on these plates below 0.1% compared to the original inoculum

Killing Curve determination

- For the determination of the killing curve of a test compound a dilution series of test compound was made and inoculated with approximately 5×10^5 CFU/ml as described for the MIC macrodilution assay above At the timepoints indicated 100 µl samples was withdrawn from the test tubes, serially diluted and spotted in duplicate on unselective agar plates to determine CFU Test compounds with bactericidal activity is capable of decreasing surviving colony counts (CFU/ml) when incubated with bacteria Bactericidal activity may be either primarily dependent on concentration of test compound or on incubation time with test compound An example of a bactericidal compound (II-105), which is primarily dependent on the concentration of the test compound is shown in Figure 3 An example of a bactericidal compound (I-056) which is primarily dependent on the incubation time with the compound is shown in Figure 4

MIC determination against Helicobacter pylori

- Six strains of *Helicobacter pylori* were used in an agar dilution assay according to the standards of NCCLS (National Committee for Clinical Laboratory Standards Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically, Approved Standard – Fifth Edition M7-A5 NCCLS 2000) MH-agar plates supplemented with 5% horse blood and containing a dilution series of the test compound were inoculated in duplicate with 10 µl spots of a 2 McF suspension of the different strains of *H pylori*. This inoculum corresponds to approximately 10E6 CFU/spot. Plates were then incubated in a microaerophilic atmosphere at 35°C for 72 hours. The MIC endpoint was determined as the lowest concentration of test compound able to completely inhibit or most significantly reduce growth compared to growth control plates not containing test compounds.

Activity determination against anaerobic bacteria

- Screening for activity against anaerobic bacteria was done against two isolates of *Bacteroides fragilis*, an isolate of *Clostridium difficile* and an isolate of *Clostridium perfringens* in an agar dilution assay as described by NCCLS (National Committee for Clinical Laboratory Standards Methods for Antimicrobial Susceptibility Testing of Anaerobic Bacteria, Approved Standard – Fifth Edition M11-A5 NCCLS 2000) with the exception that Mueller-Hinton agar was used in place of supplemented Brucella broth. Plates containing test compound at a single concentration (either 100 or 150 µM) were prepared in duplicate along with appropriate control plates. Activity was present if growth in the presence of test substance was absent or most significantly reduced compared to growth control plates not containing test compound.

25 Leishmania promastigote assay

- A WHO reference vaccine strain of *L. major* originally isolated from a patient in Iran were cultured in Medium 199 with Hanks Salts containing 0.02 mg/ml gentamycin, 25 mM HEPES, 4 mM L-glutamine, and 10% heat inactivated fetal calf serum (FCS). Incubation was carried out at 27°C. Promastigotes were harvested at day 3 of culture and used for the assay of inhibition of parasite growth.

- The effect of test compounds on promastigotes was assessed by a method modified from Pearson et al. Briefly, promastigotes (0.8×10^6 /well) were incubated in 200 µl duplicate cultures either with a dilution series of test compound or medium alone in 96 wells flat bottom microtiter plates. After 2h of incubation, 1.5 µCi of 3H-thymidine was added to each well and further incubated for 18 hours. The cultures were then harvested on Unifilter-GF/C microtiter filter plates (Packard Instruments), washed extensively and counted in a TopCount-NXT microplate scintillation counter (Packard Instruments).

40 Plasmodium falciparum assay

- Plasmodium falciparum* 3D7 was maintained in culture by a modification of the method originally described by Trager and Jensen. In brief, the parasites were grown in

- suspensions of human blood group O erythrocytes (RBC) maintained in RPMI1640 medium supplemented with 4.5 g/l Albumax II (Invitrogen), 10 mM hypoxanthine, 1.4 mM L-glutamine and 0.05 mg/ml gentamicin. Cultures were incubated at 37°C in atmosphere of 92.5% nitrogen, 5.5% carbon dioxide, and 2% oxygen. To obtain synchronized cultures of parasites erythrocytes infected with late trophozoite and schizont stages were separated from ring stages and uninfected RBC by magnet-activated cell sorting (MACS, Miltenyi BioTec) (Staalsoe, T., H.A. Giha, D. Dodoo, T.G. Theander, and L. Hviid 1999. Detection of antibodies to variant antigens on *Plasmodium falciparum*-infected erythrocytes by flow cytometry. Cytometry 35:329-336). Because of their high content of paramagnetic haemozoin, erythrocytes infected with late developmental stages of malaria parasites are specifically retained within the column. The column was washed with PBS supplemented with 2% foetal calf serum and then the column was removed from the magnet and the retained late developmental stages of parasites were eluted and cultured for an additional 18 hours. At this time the culture is highly synchronous containing more than 90% ring stages.

- These synchronized cultures of ring stage parasites were used to assay for antimalarial parasites. Briefly, cultures of ring stage parasites were adjusted to 1% parasitemia by addition of uninfected RBC. Then, these were incubated in 125 µl duplicate cultures containing 2.5×10^7 RBC/well with either a dilution series of test compound or with medium alone. Plates were then incubated at 37°C for 24 hours when cultures were labelled by the addition of 1.1 µCi 3H-phenylalanine and incubated overnight. Then, the cultures were harvested on Unifilter-GF/C microfilter plates (Packard Instruments) and washed extensively with water followed by a wash with 10% H₂O₂ to bleach hemoglobin. Filter plates were counted in a TopCount-NXT microplate scintillation counter (Packard Instruments).

DHODH Assay

- 100 µl chalcone or 0.1 M Tris-HCl pH 8.0 is added to a well in a 96-wells microtiter plate. Then 50 µl enzyme dilution is added. The microtiter plate is placed in the Powerwave_x340 and the enzymatic reactions start when adding 100 µl assay mixture. The reaction are measured every 20 sec for 10 min. The samples with chalcones are compared with the samples with 0.1 M Tris-HCl pH 8.0 and the percent inhibition is calculated.

- Enzyme dilution. The solution of recombinant purified enzyme is dissolved in 0.1 M Tris-HCl pH 8 to give an initial velocity of 0.04 - 0.05 ΔA/min.

- 2,6-dichlorophenolindophenol (DCIP)-stock solution. 40 mg DCIP and 10 ml 99 % Ethanol are mixed for 10 min at RT. Then 100 µl 1.0 M Tris-HCl pH 8 and milliQ H₂O are added to a final volume of 100 ml. The A₆₀₀ of the DCIP-stock solution are measured in a microtiter plate on the Powerwave_x340 (Bio-Tek instruments, Inc.).

Dihydroorotate dehydrogenase (DHODH)-stock solution 25 mM dihydroorotate stock-solution is prepared by first dissolving in the same amount of mol NaOH and then milliQ H₂O is added to the final volume

- 5 Assay mix (10 ml solution) 600 µl of DHODH-stock solution and X ml (depending on the A₆₀₀ value of stock-solution) DCIP to a final A₆₀₀ = 2.5 are mixed Then 0.1 M Tris-HCl pH 8.0 are added to a final volume of 10 ml

- 10 Preparation of compound solution A 10 mM stock-solution of compound (e.g. a chalcone derivative) is made in dimethylsulfoxide (DMSO) The compound is then diluted in 0.1 M Tris-HCl pH 8 to the test concentrations The final DMSO concentration in the sample is 10%

Biological Results

- 15 Licochalcone A (LicA) and 4'-methoxy chalcone (4'MC) described in WO 93/17671 are used as reference compounds in the following discussion

Activity against non-fastidious bacteria.

- 20 Licochalcone A exhibit moderate bactericidal activity against common pathogenic Gram-positive non-fastidious bacteria including *Staphylococcus aureus*, *Enterococcus faecalis*, *Enterococcus faecium*, *Streptococcus pneumoniae*, *Streptococcus pyogenes*, and *Streptococcus agalactiae* Licochalcone A maintains its activity also against antibiotic resistant bacteria, e.g. *Staphylococcus aureus* ATCC33591 (resistant to methicillin) and
- 25 *Enterococcus faecium* #17051 (resistant to vancomycin) In contrast, Licochalcone A have only modest or no activity against the prototype pathogenic Gram-negative bacterium, *Escherichia coli* 4'MC as a representative of non-hydroxyl chalcones exhibit no antibacterial effect at all

- In comparison with Licochalcone A, aminochalcones retain the activity of
- 30 Licochalcone A against pathogenic Gram-positive bacteria including antibiotic-resistant strains (cf. Table SS) Several aminochalcones exhibit increased potency against Gram-positive pathogens (e.g. II-062, II-067, II-056, II-071, II-105, II-128) In contrast to Licochalcone A, aminochalcones exhibit activity against *Escherichia coli* Thus, several aminochalcones (e.g. II-067, II-068, II-056, II-105, II-128, II-129, II-134) exhibit
- 35 considerable activity against the ESS strain of *E. coli*, which generally is more susceptible to antibiotics than the type strain *E. coli* ATCC25922 However, several aminochalcones (e.g. II-059 and II-134) exhibit similar high activity against both Gram-positive bacteria and *E. coli* ESS and ATCC 25922 strains Thus, aminochalcones can be modified to permeate and inhibit Gram-negative bacteria This indicates the potential use of aminochalcones in
- 40 the treatment of infections with Gram-negative bacteria

In the treatment of severe infections in immunocompromised patients bactericidal action of an antibiotic is a necessity As exemplified in Figures 3 and 4, aminochalcones retain the bactericidal action of Licochalcone A For some aminochalcones the bactericidal action is

predominantly dependent on the concentration of the compound (e g II-105, cf Figure 3), for others the bactericidal action is predominantly dependent on the time of incubation with the compound (e g II-056, cf Figure 4) This knowledge is helpful when designing dosing regimens for *in vivo* efficacy trials

5

Tabel SS Comparasion of the effect of amino-chalcones and Licochalcone/4'MC on bacteria, MIC values in μM

	A	B	C	D	E	F	G	H
LICA	37.5	37.5	37.5	37.5	37.5	75.0		300.0
4'-MC	NA	NA	NA	NA	NA	NA	NA	NA
II-062	9.4	9.4	9.4	9.4	9.4	37.5		75.0
II-067	9.4	9.4	9.4	18.8	18.8	18.8		18.8
II-068	9.4	9.4	18.8	18.8	9.4	18.8		18.8
II-056	9.4	9.4	9.4	9.4	9.4	18.8		18.8
II-071	4.7	9.4	4.7	9.4	9.4	75.0		150.0
II-105	9.4	9.4	18.8	4.7	4.7	2.4	75.0	9.4
II-128	9.4	9.4	18.8	18.8	9.4	18.8		9.4
II-129	18.8	37.5	37.5	37.5	37.5	37.5		18.8
II-134	18.8	18.8	18.8	18.8	18.8	18.8	37.5	18.8
II-059	37.5	37.5	37.5	18.8	18.8	18.8	18.8	18.8

A *Staphylococcus aureus* ATCC29213, **B** *Staphylococcus aureus* ATCC33591, **C**

10 *Staphylococcus intermedius* #2357 (clinical isolate from the Copenhagen area), **D**

Enterococcus faecalis ATCC29212, **E** *Enterococcus faecium* #17501 (vancomycin-resistant clinical isolate), **F** *Streptococcus pneumoniae* #998 (clinical isolate), **G** *Eschericia coli* ATCC25922 and **H** *Eschericia coli* ESS NA no activity

15

Activity against *Helicobacter pylori*

Colonization of the gastric mucosa with *Helicobacter pylori* is an important pathogenic determinant for the development of gastritis and peptic ulcer. Amino-chalcones exhibit activity against *Helicobacter pylori*. Several amino-chalcones (e g II-063, II-075, II-077, II-078, II-085, II-091, II-103, II-105) exhibit MICs in the range between 12.5 μM and 100 μM when tested against a panel of six strains *Helicobacter pylori*, that includes strains resistant to metronidazole. Metronidazole is an antibiotic commonly included in treatment regimens designed to eradicate *Helicobacter* colonization for the treatment of peptic ulcer.

25 The activity of amino-chalcones against both metronidazole-resistant and sensitive *Helicobacter pylori* clearly indicates the potential use of these compounds in the treatment of *Helicobacter* infections.

30

Activity against anaerobic bacteria

Aminochalcones have been assayed in a single concentration of compound (100 μ M) for activity against a panel of anaerobic bacteria containing common human pathogenic bacteria (*Bacteroides fragilis*, *Clostridium perfringens*, *Clostridium difficile*) Several aminochalcones (e g II-048, II-063, II-074, II-077, II-078, II-103, II-105, II-140) exhibit activity against all microorganisms within the test panel This clearly indicates the potential use of aminochalcones in treatment of infection caused by anaerobic bacteria

10 Activity against protozoa:

Activity against *Leishmania major*

Leishmania major is a protozoan parasite transmitted by the sandfly, *Phlebotomus*, and causing cutaneous leishmaniasis or kala-azar in humans Licochalcone A exhibit activity against *Leishmania* parasites and has shown efficacy in experimental animal models of cutaneous and visceral *Leishmania* infection (Chen et al , 1994) Aminochalcones exhibit activity *in vitro* against *Leishmania major* with significantly improved potency compared to Licochalcone A and 4'MC (cf Table WW) The results clearly indicate the potential use of aminochalcones in the treatment of *Leishmania* infection

Table WW Effect of amino-chalcones on *L. major*

Comp	IC ₅₀ in μ M
LICA	5.0
4'MC	5.6
II-064	0.2
II-077	0.1
II-078	0.8
II-091	0.5
II-103	0.9
II-105	0.3
II-111	0.7
II-123	0.6
II-128	1.0
II-134	0.5
II-151	0.3

25

Activity against *Plasmodium falciparum*

Plasmodium falciparum is a protozoan parasite transmitted by the mosquito, *Anopheles*, and causing malignant or severe malaria in humans Licochalcone A exhibit activity against *Plasmodium falciparum* *in vitro* and protects mice from infection with *P. yoelii* and *P. berghei*

30

(Chen et al , 1994) Amino-chalcones exhibit activity *in vitro* against *Plasmodium falciparum* and several amino-chalcones exhibit improved potency compared to Licochalcone A (cf Table TT and Figure 5) The results clearly indicate the potential use of amino-chalcones in the treatment of malaria

5

Table TT Activity against *Plasmodium falciparum* 3D7

Comp	IC ₅₀ in μ M
LICA	5 0
4'MC	40.0
II-064	0 7
II-111	0 5
II-155	0 6
II-123	0 1
II-124	0 2
II-134	1 0
II-140	1 0
II-046	4 4
II-059	3 1
II-070	3 8
II-091	1 4
II-139	4 3

Metabolism

- The usefulness of chalcones as drug candidates have been limited by the metabolism of the compounds resulting in short half-lives *in vivo* (Lica 100% turn-over *in vitro* and $t_{1/2}$ = 10min *in vivo*)

- The introduction of an amino group in the chalcone changes the metabolic properties, this is clear from Table QQ where the metabolic turn-over of a number of amino-chalcones are compared to Lica The amino-chalcones prepared are expected to show low or no metabolism *in vivo* as the metabolic turn-over are between 0-10% (compared to 100% turn-over for Lica) Consequently, the half-life of an amino-chalcone will be longer, reducing the dose needed for treatment

20 Table QQ Metabolic turn-over *in vitro* (%)

LICA	100 0
II-039	3 4
II-042	0 7
II-047	0 0
II-055	0 0
II-056	8 0

II-060 0 0
 II-065 6 0
 II-066 0 0
 II-067 0 0

Inhibition of DHODH

Several of the amino-chalcones prepared are potent inhibitors of DHODH. The compounds
 5 are as potent as LicA and by far more potent than ordinary chalcones exemplified by 4'MC

Table DD Inhibition of DHODH

Comp	Inhibition (%)
LICA	24.5
4'MC	7.0
II-057	23
II-058	27
II-059	27.5
II-062	26
II-075	26
II-078	21.5
II-085	20

10 Solubility

The solubility of the neutral chalcones described in WO 93/17671 is very low. A representative chalcone 4'-methoxy-chalcone has a solubility of <0.05 mg/ml. A few chalcones have a higher solubility due to (metabolically unstable) hydroxyl groups in the molecule. LicA has a solubility of 0.2 mg/ml.

15

The amino-chalcones described in this application are by far superior having solubility numbers in mg/ml. Examples are

II-042 >6 mg/ml,
 20 II-047 10.0 mg/ml,
 II-089 6.3 mg/ml

The high solubility means that dissolution and hence absorption will be no problem. This will inevitably cause a dramatic reducing of the dose needed making the amino-chalcones
 25 very usable as drug candidates.

Conclusion The use of chalcones as drug candidates for the treatment of parasitic or bacterial infections have been limited by the low in vivo potency (50 mg/kg for LicA) of the compounds and a narrow spectrum of activity.

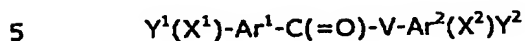
Several factors contribute to the low in vivo potency Fast metabolism resulting in short half-lives in vivo, Low/no solubility in the intestine and consequently low/no absorption, Medium potency of the compounds against parasites and no activity against bacteria

5 (except for LicA)

The amino-chalcones in this application are expected to fulfill the criteria for a drug candidate The metabolism is low, the solubility is high and the compounds are potent against parasites as well as (resistant) Gram positive and Gram negative bacteria

CLAIMS

1 A compound of the general formula



wherein Ar^1 and Ar^2 independently are selected from aromatic rings (aryl) and heteroaromatic rings (heteroaryl),

10 V designates $-CH_2-CH_2-$, $-CH=CH-$ or $-C\equiv C-$, preferably $-CH=CH-$,

one or both of Y^1 and Y^2 independently represent at least one, such as 1-2, e.g. one, diamino-functional substituent(s) of the formula



wherein Z is a biradical $-(C(R^H)_2)_n-$, wherein n is an integer in the range of 1-6, preferably 1-4, such as 1-3, and each R^H is independently selected from hydrogen and C_{1-6} -alkyl, or two R^H on the same carbon atom may designate $=O$,

20 R^1 and R^2 independently are selected from hydrogen, optionally substituted C_{1-12} -alkyl, optionally substituted C_{2-12} -alkenyl, optionally substituted C_{4-12} -alkadienyl, optionally substituted C_{6-12} -alkatrienyl, optionally substituted C_{2-12} -alkynyl, optionally substituted C_{1-12} -alkoxycarbonyl, optionally substituted C_{1-12} -alkylcarbonyl, optionally substituted aryl, 25 optionally substituted aryloxycarbonyl, optionally substituted arylcarbonyl, optionally substituted heteroaryl, optionally substituted heteroaryloxycarbonyl, optionally substituted heteroarylcarbonyl, aminocarbonyl, mono- and di(C_{1-6} -alkyl)aminocarbonyl, amino- C_{1-6} -alkyl-aminocarbonyl, mono- and di(C_{1-6} -alkyl)amino- C_{1-6} -alkyl-aminocarbonyl, or R^1 and R^2 together with the nitrogen atom to which they are attached ($-N(R^1)R^2$) form an optionally 30 substituted nitrogen-containing heterocyclic ring,

X^1 and X^2 independently designates 0-5, preferably 0-4, such as 0-3, e.g. 0-2, substituents, where such optional substituents independently are selected from optionally substituted C_{1-12} -alkyl, optionally substituted C_{2-12} -alkenyl, optionally substituted C_{4-12} -alkadienyl, optionally substituted C_{6-12} -alkatrienyl, optionally substituted C_{2-12} -alkynyl, 35 hydroxy, optionally substituted C_{1-12} -alkoxy, optionally substituted C_{2-12} -alkenyloxy, carboxy, optionally substituted C_{1-12} -alkoxycarbonyl, optionally substituted C_{1-12} -alkylcarbonyl, formyl, C_{1-6} -alkylsulphonylamino, optionally substituted aryl, optionally substituted aryloxycarbonyl, optionally substituted aryloxy, optionally substituted 40 arylcarbonyl, optionally substituted arylamino, arylsulphonylamino, optionally substituted heteroaryl, optionally substituted heteroaryloxycarbonyl, optionally substituted heteroaryloxy, optionally substituted heteroarylcarbonyl, optionally substituted heteroarylamino, heteroarylsulphonylamino, optionally substituted heterocyclyl, optionally

substituted heterocyclyloxycarbonyl, optionally substituted heterocyclyloxy, optionally substituted heterocyclylcarbonyl, optionally substituted heterocyclylamino, heterocyclylsulphonylamino, amino, mono- and di(C₁₋₆-alkyl)amino, carbamoyl, mono- and di(C₁₋₆-alkyl)aminocarbonyl, amino-C₁₋₆-alkyl-aminocarbonyl, mono- and di(C₁₋₆-alkyl)amino-C₁₋₆-alkyl-aminocarbonyl, C₁₋₆-alkylcarbonylamino, amino-C₁₋₆-alkyl-carbonylamino, mono- and di(C₁₋₆-alkyl)amino-C₁₋₆-alkyl-carbonylamino, cyano, guanidino, carbamido, C₁₋₆-alkanoyloxy, C₁₋₆-alkylsulphonyl, C₁₋₆-alkylsulphinyl, C₁₋₆-alkylsulphonyloxy, aminosulfonyl, mono- and di(C₁₋₆-alkyl)aminosulfonyl, nitro, optionally substituted C₁₋₆-alkylthio, and halogen, where any nitrogen-bound C₁₋₆-alkyl may be substituted with hydroxy, C₁₋₆-alkoxy, C₂₋₆-alkenyloxy, amino, mono- and di(C₁₋₆-alkyl)amino, carboxy, C₁₋₆-alkylcarbonylamino, halogen, C₁₋₆-alkylthio, C₁₋₆-alkyl-sulphonyl-amino, or guanidine,

and salts thereof

15 2 The compound according to claim 1, wherein R¹ and R² independently are selected from hydrogen, optionally substituted C₁₋₁₂-alkyl, optionally substituted C₂₋₁₂-alkenyl, optionally substituted C₂₋₁₂-alkynyl, optionally substituted C₁₋₁₂-alkylcarbonyl, arylcarbonyl, heteroarylcarbonyl, aminocarbonyl, mono- and di(C₁₋₆-alkyl)aminocarbonyl, amino-C₁₋₆-alkyl-aminocarbonyl, and mono- and di(C₁₋₆-alkyl)amino-C₁₋₆-alkyl-aminocarbonyl

20

3 The compound according to any of the preceding claims, wherein X¹ and X² independently designates 0-4, such as 0-3, e.g. 0-2, substituents, where such optional substituents independently are selected from optionally substituted C₁₋₁₂-alkyl, hydroxy, optionally substituted C₁₋₁₂-alkoxy, optionally substituted C₂₋₁₂-alkenyloxy, carboxy, optionally substituted C₁₋₁₂-alkylcarbonyl, formyl, C₁₋₆-alkylsulphonylamino, optionally substituted aryl, optionally substituted aryloxycarbonyl, optionally substituted aryloxy, optionally substituted arylcarbonyl, optionally substituted arylamino, arylsulphonylamino, optionally substituted heteroaryl, optionally substituted heteroarylamino, optionally substituted heteroarylcarbonyl, optionally substituted heteroaryloxy, heteroarylsulphonylamino, optionally substituted heterocyclyl, optionally substituted heterocyclyloxy, optionally substituted heterocyclylamino, amino, mono- and di(C₁₋₆-alkyl)amino, carbamoyl, mono- and di(C₁₋₆-alkyl)aminocarbonyl, amino-C₁₋₆-alkyl-aminocarbonyl, mono- and di(C₁₋₆-alkyl)amino-C₁₋₆-alkyl-aminocarbonyl, C₁₋₆-alkylcarbonylamino, amino-C₁₋₆-alkyl-carbonylamino, mono- and di(C₁₋₆-alkyl)amino-C₁₋₆-alkyl-carbonylamino, guanidino, carbamido, C₁₋₆-alkylsulphonyl, C₁₋₆-alkylsulphinyl, C₁₋₆-alkylsulphonyloxy, optionally substituted C₁₋₆-alkylthio, aminosulfonyl, mono- and di(C₁₋₆-alkyl)aminosulfonyl, and halogen, where any nitrogen-bound C₁₋₆-alkyl may be substituted with hydroxy, C₁₋₆-alkoxy, and/or halogen

40 4 The compound according to any of the preceding claims, wherein R¹ and R² independently are selected from hydrogen, optionally substituted C₁₋₆-alkyl, optionally substituted C₁₋₆-alkylcarbonyl, heteroarylcarbonyl, aminocarbonyl, mono- and di(C₁₋₆-alkyl)aminocarbonyl, amino-C₁₋₆-alkyl-aminocarbonyl, mono- and di(C₁₋₆-alkyl)amino-C₁₋₆-alkyl-aminocarbonyl

- 5 The compound according to any of the preceding claims, wherein X^1 and X^2 independently designates 0-3, e g 0-2, substituents, where such optional substituents independently are selected from optionally substituted C_{1-6} -alkyl, hydroxy, optionally substituted C_{1-6} -alkoxy, carboxy, optionally substituted C_{1-6} -alkylcarbonyl, C_{1-6} -alkylsulphonylamino, optionally substituted aryl, optionally substituted aryloxy, optionally substituted arylamino, arylsulphonylamino, optionally substituted heteroaryl, optionally substituted heteroarylamino, heteroarylsulphonylamino, amino, mono- and di(C_{1-6} -alkyl)amino, carbamoyl, C_{1-6} -alkylcarbonylamino, guanidino, carbamido, optionally substituted C_{1-6} -alkylthio, optionally substituted heterocyclyl, optionally substituted heterocyclioxy, optionally substituted heterocyclylamino and halogen, where any nitrogen-bound C_{1-6} -alkyl may be substituted with hydroxy, C_{1-6} -alkoxy, and/or halogen
- 6 The compound according to any of the preceding claims, wherein V designates
- 15 $-\text{CH}=\text{CH}-$
-
- 7 The compound according to any of the preceding claims, wherein at least one of Ar^1 and Ar^2 , preferably both, are aromatic rings, in particular phenyl rings
- 20 8 The compound according to claim 7, wherein both of Ar^1 and Ar^2 are phenyl rings and Y^1 represent at least one diamino-functional substituent
- 9 The compound according to any of the preceding claims, wherein X^2 represents at least one substituent selected from C_{1-6} -alkyl, C_{1-6} -alkoxy, C_{1-6} -alkylcarbonyl, optionally substituted aryl, optionally substituted aryloxy, optionally substituted arylamino, optionally substituted heteroaryl, optionally substituted heteroarylamino, mono- and di(C_{1-6} -alkyl)amino, C_{1-6} -alkylcarbonylamino, optionally substituted C_{1-6} -alkylthio, optionally substituted heterocyclyl, optionally substituted heterocyclioxy, optionally substituted heterocyclylamino and halogen
- 25 30 10 The compound according to any of the preceding claims, wherein at least one or Ar^1 and Ar^2 is selected from thiazolyl, pyrrolyl, imidazolyl, pyrazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, thiophenyl, quinolyl, isoquinolyl, and indolyl
- 35 11 The compound according to any of the preceding claims, wherein Z is $-(\text{CH}_2)_n-$ wherein n is 1-4, such as 1-3
- 12 The compound according to any of the preceding claims, wherein one of Y^1 and Y^2 represent a substituent of the formula
- 40 $-\text{CH}_2-\text{N}(\text{R}^1)\text{R}^2$
- wherein R^1 and R^2 is selected from hydrogen and C_{1-6} -alkyl

- 13 A compound according to claim 14, wherein V is -CH=CH-, and Ar¹ and Ar² both are phenyl rings
- 14 A compound according to any of claims 13 and 14, wherein Y¹ represents the
5 substituent of the formula -CH₂-N(R¹)R²
- 15 A pharmaceutical composition comprising a compound as defined in any of the claims 1-14 in combination with a pharmaceutically acceptable carrier
- 10 16 A compound as defined in any of claims 1-14 for use as a drug substance
- 17 The use of a compound as defined in any of the claims 1-14 for the preparation of a pharmaceutical composition for the treatment of bacterial infections in a mammal in need thereof
- 15 18 The use according to claim 17, wherein the bacterial infection is caused by a bacteria selected from Gram-positive bacteria, Gram-negative bacteria, microaerophilic bacteria, and anerobic bacteria
- 20 19 The use according to claim 18, wherein the bacteria is a microaerophilic bacteria, e g a bacteria associated with gastric disease, such as *Helicobacter pylori*
- 20 The use according to claim 18, wherein the bacteria is selected from antibiotic-sensitive and -resistant strains of *S aureus*
- 25 21 The use according to claim 18, wherein the bacteria is selected from antibiotic-sensitive and -resistant strains of *E faecium*
- 22 The use according to claim 18, wherein the bacteria is selected from a *S pneumoniae*
30 and *S pyogenes*
- 23 The use according to claim 18, wherein the bacteria is a member of *Enterobacteriaceae*, e g *E coli*
- 35 24 The use according to claim 18, wherein the bacteria is a pathogenic anaerobic bacteria, e g *Bacteroides fragilis* or *Clostridium species*
- 25 The use of a compound as defined in any of claims 1-14, for the preparation of a pharmaceutical composition for the treatment of infections caused by protozoa in a
40 mammal
- 26 The use according to claim 25, wherein the infection is caused by a protozoa selected from *Plasmodium falciparum*, *Plasmodium vivax*, *Plasmodium ovale* and *Plasmodium malanae*

27 The use of a compound as defined in any of the claims 1-14, for the preparation of a pharmaceutical composition for the treatment of infections in a mammal caused by *Leishmania spp*

5

28 The use according to claim 27, wherein the infection is cutaneous and/or visceral

29 A method of predicting whether a chemical compound has a potential inhibitory effect against a microorganism selected from *Helicobacter pylori* and *Plasmodium falciparum*,

10 said method comprising preparing a mixture of a dihydroorotate dehydrogenase, a substrate for dihydroorotate dehydrogenase and the chemical compound, measuring the enzymatic activity of dihydroorotate dehydrogenase (A), comparing the enzymatic activity of dihydroorotate dehydrogenase (A) with the standard activity of dihydroorotate dehydrogenase (B) corresponding to the activity of a dihydroorotate dehydrogenase in a

15 similar sample, but without the chemical compound, predicting that the chemical compound has a potential inhibitory effect against *Helicobacter pylori* and *Plasmodium falciparum* if A is significantly lower than B

30 The method according to claim 29, wherein the chemical compound is a chalcone

20 dervative

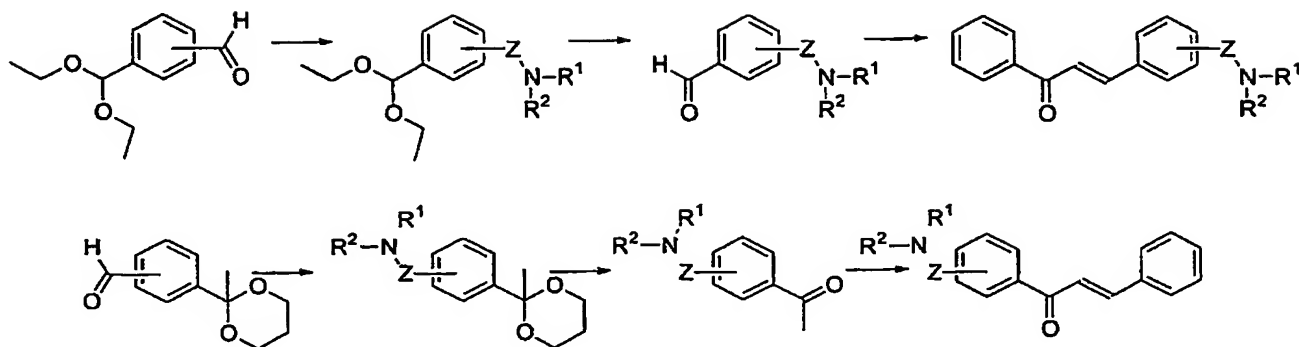
31 The method according to claim 30, wherein the chemical compound is a chalcone derivative as defined in any of the claims 1-14

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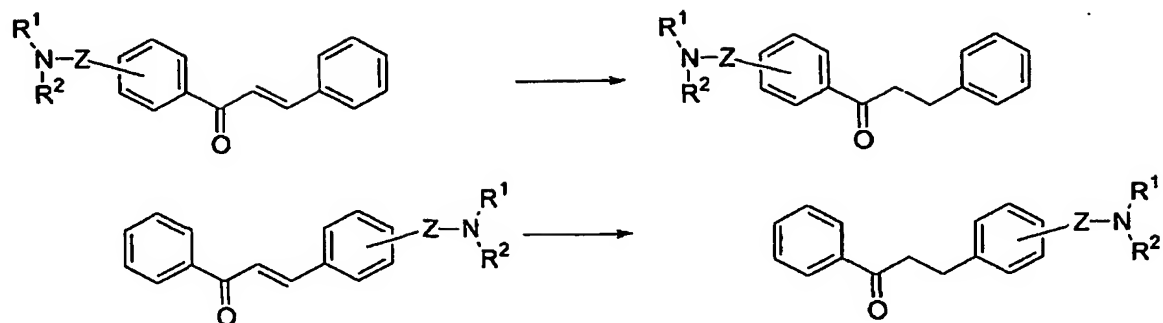
Figure 1



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Figure 2



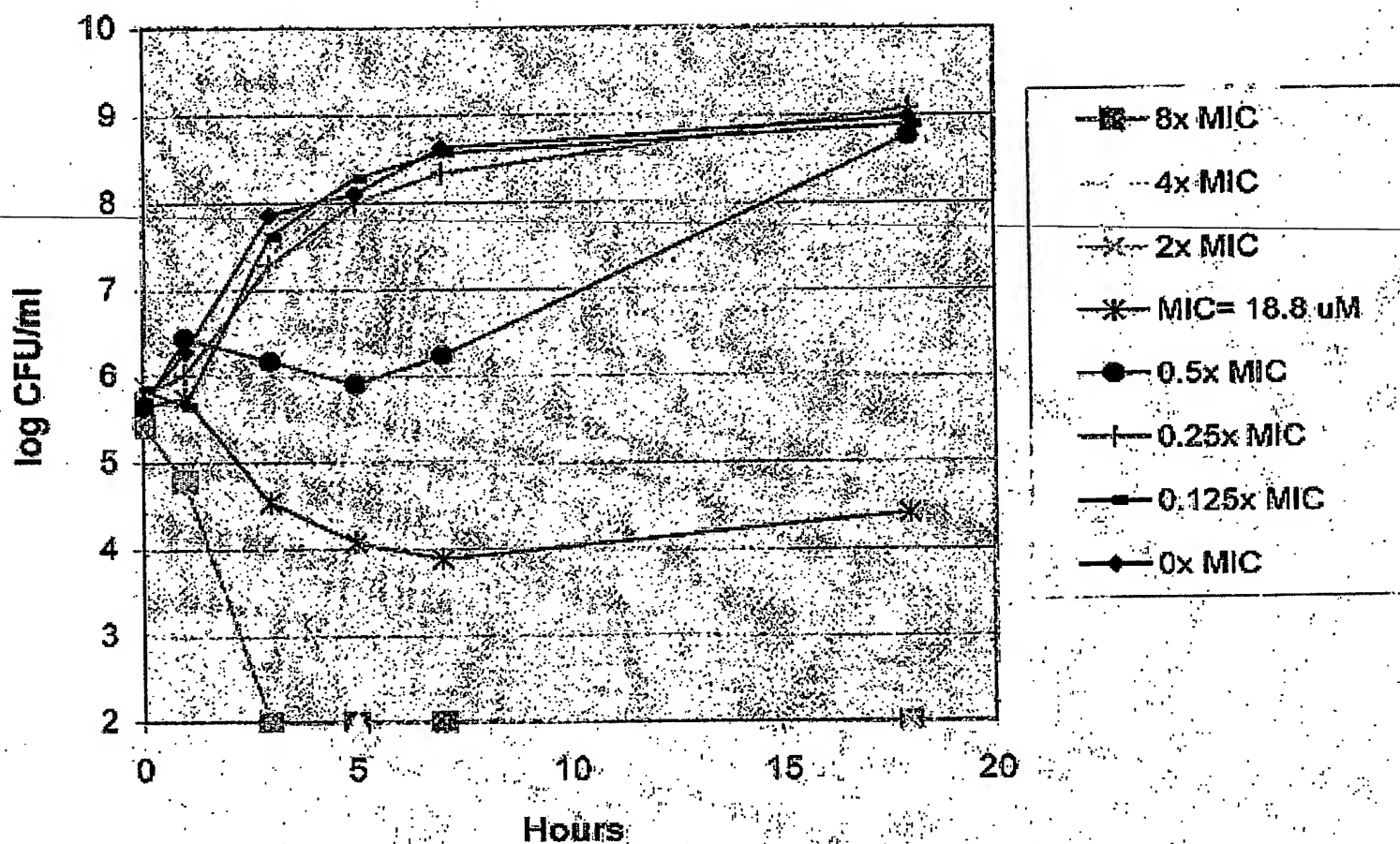
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Figure 3

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The graph illustrates the effect of gentamicin concentration on bacterial growth over 20 hours. The y-axis represents log CFU/ml, ranging from 2 to 9. The x-axis represents time in hours, ranging from 0 to 20. The legend identifies eight data series: 16x MIC (open squares), 8x MIC (open circles), 4x MIC (asterisks), 2x MIC (asterisks), MIC=9.4 μM (filled circles), 0.5x MIC (plus signs), 0.25x MIC (filled squares), and 0x MIC (filled diamonds). The 16x MIC series shows the most rapid and sustained reduction in bacterial load, reaching a minimum of approximately 2.1 log CFU/ml at 7 hours. The 8x MIC and 4x MIC series also show significant and sustained reductions. The 2x MIC series shows a transient reduction followed by regrowth. The MIC=9.4 μM series shows a transient reduction followed by regrowth. The 0.5x MIC series shows a transient reduction followed by regrowth. The 0.25x MIC series shows a transient reduction followed by regrowth. The 0x MIC series shows no reduction in bacterial load.

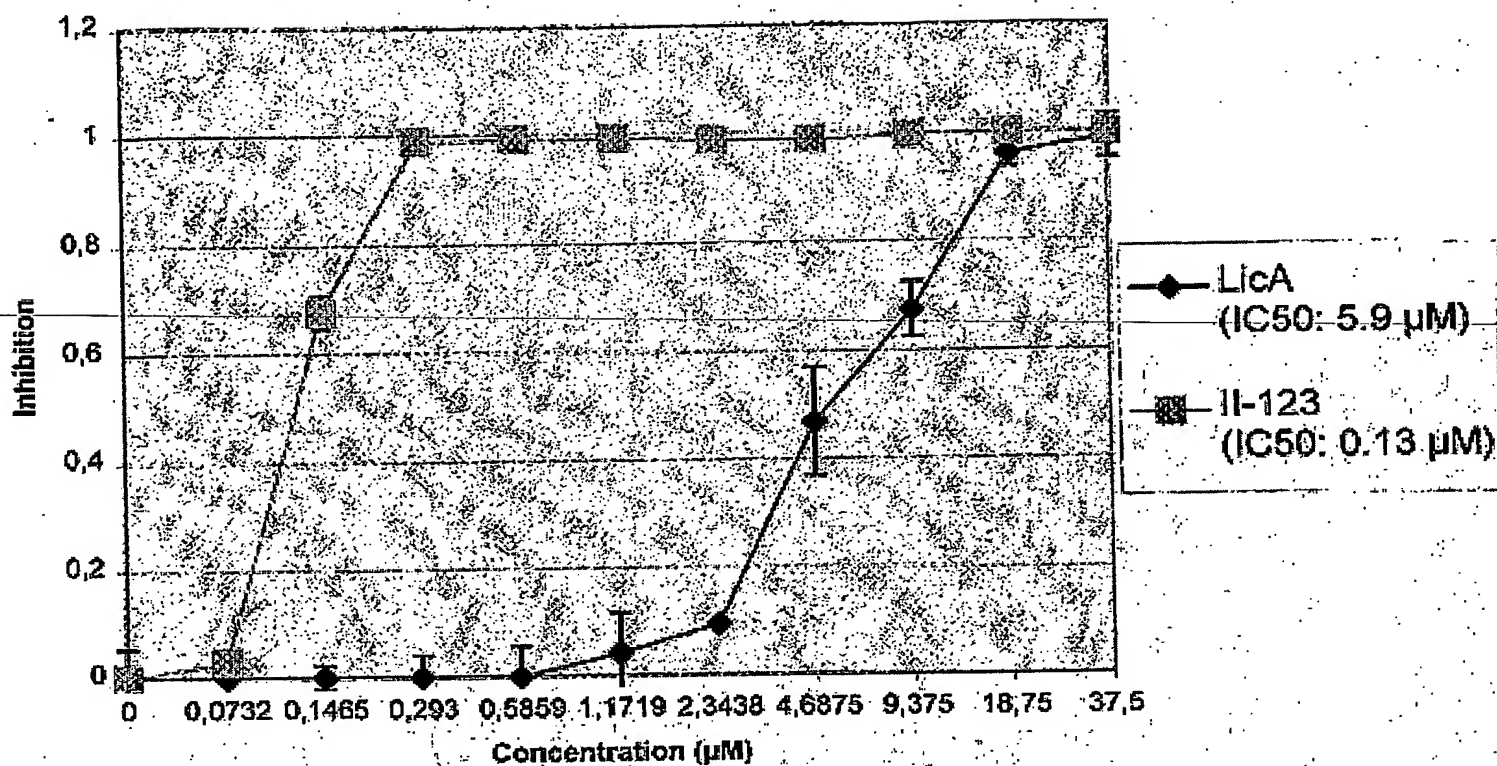
Hours	16x MIC	8x MIC	4x MIC	2x MIC	MIC=9.4 μM	0.5x MIC	0.25x MIC	0x MIC
0	5.5	5.8	6.0	5.8	5.5	5.8	5.5	5.8
1	4.8	5.2	5.0	5.8	5.7	5.8	5.5	6.3
3	3.5	4.3	4.4	5.8	5.6	5.8	5.5	7.9
5	2.3	2.9	3.0	6.2	4.9	6.2	5.5	8.5
7	2.1	2.1	2.1	6.8	4.0	6.8	5.5	8.6
18	2.1	2.1	2.1	4.0	5.2	4.0	2.1	8.7

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